In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: December 14, 2020

AUTUMN DECKER,	*	No. 15-017V
Petitioner,	*	Special Master Sanders
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Ruling on Entitlement; Hepatitis A Vaccine ("HAV"); Hashimoto's thyroiditis; Premature Ovarian Failure ("POF").
Respondent.	*	

Andrew Downing, Van Cott & Talamante, PLLC, Phoenix, AZ, for Petitioner.
Lara Englund, U.S. Department of Justice, Washington, DC, for Respondent.

RULING ON ENTITLEMENT[1]

On January 7, 2015, Candie Decker, mother of Autumn Decker ("Petitioner"), filed a petition pursuant to the National Vaccine Injury Compensation Program.[2] Pet. at 1, ECF No. 1. On October 25, 2017, Petitioner attained the age of majority, and the caption was appropriately amended. ECF No. 79. Petitioner alleged that the Hepatitis A vaccine ("HAV") she received on July 16, 2013, caused her to suffer from Hashimoto's thyroiditis[3] and premature ovarian failure ("POF")[4]. Pet. at 1–5.

[1] This Ruling shall be posted on the website of the United States Court of Federal Claims, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2012)). **This means the Ruling will be available to anyone with access to the Internet.** As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b).

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. (hereinafter "Vaccine Act," "the Act," or "the Program").

[3] Hashimoto's thyroiditis is also called Hashimoto's disease, which is "a progressive type of autoimmune thyroiditis with lymphocytic infiltration of the gland and circulating antithyroid antibodies; patients have goiter and gradually develop hypothyroidism . . ." *Dorland's Illustrated Medical Dictionary* 1263, 535 (32nd ed. 2012) [hereinafter "*Dorland's*"].

[4] POF is sometimes referred to as Primary Ovarian Insufficiency ("POI") or premature menopause. POF is defined as the "premature cessation of ovulation [and] the absence or irregularity of menses lasting at least four months, with menopausal levels of serum gonadotropins, in an adolescent girl or woman under 40 years of age. It may be temporary or permanent." *Dorland's* at 1135.

After carefully analyzing and weighing all the evidence and testimony presented in this case in accordance with the applicable legal standards, I find that Petitioner is entitled to compensation.

I. Procedural History

On January 7, 2015, the petition in the above captioned case was filed for compensation. *See* Pet. at 1. Over the next six months, Petitioner filed her medical records and a statement of completion. Pet'r's Exs. 1–15, ECF Nos. 7, 11, 15, 18–20. Respondent then filed a Rule 4(c) report on July 6, 2015, recommending that compensation be denied. ECF No. 21. A status conference was held on July 15, 2015, at which time Petitioner was directed to submit an expert report in support of her claim by July 29, 2015. ECF No. 22.

Petitioner submitted an initial expert report from James Wheeler, M.D., J.D., on July 21, 2015. Pet'r's Ex. 16, ECF No. 23-1. Petitioner filed supporting medical articles and additional medical records on August 7, 2015. Pet'r's Exs. 19–30, ECF Nos. 24–26. On December 4, 2015, Respondent filed two responsive reports, one from David Frankfurter, M.D., and one from Patrizio Caturegli, M.D. Resp't's Exs. A, C, ECF Nos. 30-1, 30-3. Petitioner filed a supplemental expert report from Dr. Wheeler, along with additional medical literature, on January 15, 2016. Pet'r's Exs. 31–49, ECF Nos. 32, 33. On June 27, 2016, Petitioner filed a report authored by a second expert, Yehuda Shoenfeld, M.D. Pet'r's Ex. 50, ECF No. 43-1. Respondent filed a responsive expert report from Dr. Caturegli on October 3, 2016. Resp't's Ex. E, ECF No. 50-1.

Respondent retained a third expert, Edward Cetaruk, M.D., and filed Dr. Cetaruk's expert report and supporting medical literature on March 16, 2017. Resp't's Exs. F–H, ECF Nos. 64–66. Petitioner thereafter filed a responsive report from a third expert, Steven Pike, M.D., J.D., on June 29, 2017. Pet'r's Ex. 92, ECF No. 71-1. Petitioner filed accompanying medical literature on July 6, 2017. Pet'r's Exs. 94–110, ECF Nos. 73–74. Respondent filed a final responsive report from Dr. Cetaruk on September 18, 2017. Resp't's Ex. I, ECF No. 77. From November 20, 2017, through March 19, 2019, Petitioner continued to file additional medical records. Pet'r's Exs. 111–132, ECF Nos. 81, 88, 106, 108, 109, 115.

On April 12, 2018, I set this matter for hearing on February 26–28, 2019. ECF Nos. 82, 85. The parties completed the pre-hearing filings by early February 2019, ECF Nos. 85–87, 89–91, and the hearing was held as scheduled. *See* Min. Entry, docketed Mar. 5, 2019. Post-hearing briefs were filed on June 7, 2019, September 5, 2019, and October 7, 2019, respectively. ECF Nos. 125, 127, 132.

This matter is ripe for consideration.

II. Factual Background

a. Medical Records

Petitioner was born on October 25, 1999. Pet'r's Ex. 3 at 1, ECF No. 7-3. Petitioner's family history is notable for Hashimoto's thyroiditis, Turner Syndrome,[5] and type 1 diabetes mellitus[6] on her mother's side. Pet'r's Ex. 3 at 44; Pet'r's Ex. 8 at 5, ECF No. 7-8; Pet'r's Ex. 13 at 3, ECF No. 15-2; Pet'r's Ex. 14 at 6, ECF No. 18-1; Pet'r's Ex. 118 at 2, ECF No. 88-2. Petitioner's medical history is significant for sepsis[7] at birth, dermatitis,[8] proteinuria,[9] and psoriasis.[10] Pet'r's Ex. 3 at 1; Pet'r's Ex. 14 at 11; Pet'r's 119 at 6, ECF No. 88-3. On July 11, 2013, Petitioner presented to her pediatrician, William Gerba, M.D., for a thirteen-year, well-child examination. Pet'r's Ex. 3 at 69–73. At this visit, Dr. Gerba found Petitioner to be in good health. *Id.* at 72. Petitioner's developmental and physical examinations were normal. *Id.* Dr. Gerba requested that Petitioner "[r]eturn to [the] clinic in [three] months for a flu shot or earlier for Hepatitis A vaccine." *Id.* at 73.

On July 16, 2013, Petitioner returned to the clinic and received HAV in her upper left arm. Pet'r's Ex. 2 at 1, ECF No. 7-2. Petitioner was counseled about the risks and benefits of the vaccine at this visit. *Id.*

Petitioner's mother spoke with Dr. Gerba over the telephone on August 30, 2013. Pet'r's Ex. 3 at 63. During this call, Petitioner's mother reported that Petitioner was experiencing "recent onset of [dysfunctional uterine bleeding] ([three] episodes a month of bleeding)." *Id.* Dr. Gerba commented that he "would expect more regularity" as Petitioner had experienced menarche at age eleven. *Id.* He recommended a hormone panel and possible evaluation by an adolescent gynecology specialist. *Id.* Petitioner followed up with Dr. Gerba on September 3, 2013, for a physical exam and lab work. *Id.* at 61. At this visit, Petitioner reported "[two] regular menses and one brief [third] episode in August [with] no pain [and] no other bleeding." *Id.* at 55. Petitioner's physical examination and lab work were unremarkable. *Id.* at 55–58.

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[5] Turner Syndrome is "a disorder of gonadal differentiation in patients phenotypically female, marked by short stature, undifferentiated (streak) gonads, and variable abnormalities that may include webbing of the neck, low posterior hairline, cubitus valgus, and cardiac defects . . . can also be called *gonadal dysgenesis*." *Dorland's* at 1851 (emphasis in original).

[6] Type 1 diabetes mellitus is "one of the two major types of diabetes mellitus: an autoimmune disease that results in the destruction beta cells of the pancreas, leading to loss of the ability to secrete insulin . . . [i]t is characterized by abrupt onset of symptoms, insulinopenia, and dependence on exogenous insulin to sustain life; peak age of onset is 12 years, although onset can be at any age . . ." *Dorland's* at 506.

[7] Sepsis is defined as "the presence in the blood or other tissues of pathogenic microorganisms or their toxins." *Dorland's* at 1693.

[8] Dermatitis is generally defined as "inflammation of the skin." *Dorland's* at 494–96.

[9] Proteinuria is defined as "excessive serum proteins in the urine, such as in renal disease, after strenuous exercise, and with dehydration." *Dorland's* at 1535.

[10] Psoriasis is a skin condition distinct for "squamous dermatoses with variable symptoms and courses; some are inherited. Principal histological findings are Munro micro[]abscesses and spongiform pustules; also seen are rounded, circumscribed, erythematous, dry, scaling patches of various sizes, covered by gray, silvery, or white, umbilicated, lamellar scales . . ." *Dorland's* at 1547.

On February 17, 2014, Petitioner returned to Dr. Gerba. *Id.* at 43–44. Petitioner reported that her last menstrual period was at the end of December, that she had had hot flashes "several times a day for the past two weeks," and that she is "under stress at school." *Id.* at 44. Dr. Gerba also noted that under Petitioner's family history, Petitioner's mom has a hypothyroid disease.[11] *Id.* At this visit, Petitioner's physical examination was normal, and she received an intranasal flu vaccination. *Id.* at 45. Petitioner also had bloodwork done, which showed elevated postmenopausal follicle stimulating hormone ("FSH")[12] and luteinizing hormone ("LH")[13] levels, and low estradiol[14] levels.[15] *Id.* at 49. Dr. Gerba diagnosed Petitioner with secondary amenorrhea.[16] *Id.* at 45.

Petitioner presented to Benjamin Goldman, M.D., for a pelvic sonogram on February 21, 2014. Pet'r's Ex. 7 at 15, ECF No. 7-7. During the sonogram, "no cystic or solid masses were seen in the ovaries. No adnexal mass[17] [was] present." *Id.* Five days later, Petitioner presented to pediatric endocrinologists, Graeme Frank, M.D., and Allison Bauman, D.O., for lab work and consolation. Pet'r's Ex. 7 at 1–2; Pet'r's Ex. 118 at 13–17. During this visit, potential causes of POF were discussed. Pet'r's Ex. 118 at 15. The bloodwork results showed positive thyroid peroxidase,[18] elevated thyroid stimulating hormone ("TSH"),[19] negative adrenal antibodies,

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[11] Hypothyroid disease is sometimes called "hypothyroidism." It is defined as "deficiency of thyroid activity, characterized by decrease in basal metabolic rate, fatigue, and lethargy; if untreated, it progresses to myxedema." *Dorland's* at 907.

[12] Follicle stimulating hormone ("FSH") is "an anterior pituitary hormone…a glycopeptide of about 30,000 daltons that stimulates the growth and maturation of ovarian follicles, stimulates estrogen secretion, promotes the endometrial changes characteristic of the first portion (proliferative phase) of the mammalian menstrual cycle, and stimulates spermatogenesis in the male." *Dorland's* at 870.

[13] Luteinizing hormone ("LH") is "a glycoprotein anterior pituitary hormone that is a gonadotropin (28,000 daltons) and acts with follicle-stimulating hormone to promote ovulation as well as secretion of androgens and progesterone. It instigates and maintains the second (secretory) portion of the mammalian estrus and menstrual cycle . . ." *Dorland's* at 870.

[14] Estradiol is "the most potent naturally occurring ovarian and placental estrogen in mammals; it prepares the uterus for implantation of the fertilized oocyte and promotes the maturation and maintenance of the female accessory reproductive organs and secondary sex characters. It has also been produced semi[-]synthetically . . . a preparation of this hormone used in estrogen replacement therapy for conditions such as female hypogonadism, ovariectomy, or primary ovarian failure…" *Dorland's* at 649.

[15] Petitioner's FSH, LH, and estradiol levels were 116.7 IU/L, 53.4 IU/L, and 10 pg/mL, respectively; the postmenopausal ranges are 25.8-134.8 IU/L, 7.7-58.5 IU/L, 0pg/mL–46pg/mL, respectively. *See* Pet'r's Ex. 3 at 49.

[16] Secondary amenorrhea is defined as the "cessation of menstruation after it has once been established at puberty." *Dorland's* at 59.

[17] An adnexal mass is "a growth that occurs in or near the uterus, ovaries, fallopian tubes, and the connecting tissues. They are usually benign but are sometimes cancerous. Some of them are filled with fluid, and some are solid." *Adnexal Mass,* HEALTHLINE, https://www.healthline.com/health/adnexal-mass (last visited Nov. 3, 2020).

[18] Thyroid peroxidase, also called thyroperoxidase or iodide peroxidase, is an enzyme produced by the thyroid gland. "Deficiency of the enzyme…results in congenital goiter." *Dorland's* at 956.

[19] Thyroid stimulating hormone ("TSH") is also called thyrotropin and is defined as "a glycoprotein anterior pituitary hormone . . . that promotes the growth of, sustains, and stimulates hormonal secretion of the thyroid gland." *Dorland's* at 1926.

negative Fragile X screening,[20] negative celiac screening,[21] and negative ovarian antibody screens. *Id.* at 2–14; Pet'r's Ex. 8 at 4. Additionally, Petitioner's chromosomal analysis "revealed an apparently normal karyotype with no consistent numerical or structural chromosomal abnormalities." Pet'r's Ex. 7 at 14.

On March 12, 2014, Petitioner presented to Claudia Cook, M.D., an alternative medicine physician, to get a second opinion on "[p]rimary ovarian insufficiency, no menses since [December of 2013], hot flashes, [and] palpitations." Pet'r's Ex. 11 at 9, ECF No. 11-1. Petitioner's mother reported that her daughter missed her period for one month and saw the pediatrician after experiencing hot flashes and palpitations. *Id*. Petitioner reported that she began experiencing hot flashes approximately one month earlier while "studying and doing homework," which interfered with her ability to focus. *Id*. at 9–10. Petitioner also reported inadequate sleep from doing homework at late hours, several episodes of sharp [right lower quad] pain over an area "the size of a golf ball," and two-to-three episodes of sharp pain over her left ear. *Id.* at 10. A physical exam revealed an enlarged right-sided thyroid lobe. *Id*. at 11. Dr. Cook wrote that she suspected Petitioner had "suddenly escalating hypothyroidism linked to Hashimoto's [thyroiditis]" and possibly an "iodine deficiency" that led to POI. *Id*. at 12. Dr. Cook further opined that Petitioner's condition is due to multiple factors like diet, stress, electromotive force, and even the cellphone against Petitioner's body could have contributed to her problems. *Id.* Dr. Cook diagnosed Petitioner with an unspecified disorder of the thyroid, thyroid gland disorder,[22] autoimmune disease, and mineral deficiency. *Id*. at 11.

The next day, Petitioner presented to Owen Davis, M.D., a reproductive endocrinologist, for lab work. Pet'r's Ex. 8 at 4; Pet'r's Ex. 10 at 1–3, ECF No. 7-10. The lab work revealed an abnormal antinuclear antibody ("ANA") screening,[23] a negative Fragile X chromosome study, a normal anti-Müllerian hormone titer,[24] and a normal erythrocyte sedimentation rate.[25] Pet'r's Ex.

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[20] Fragile X screening tests for fragile X syndrome, "an X-linked syndrome associated with a fragile site at locus Xq27.3, characterized by intellectual disability, enlarged testes, high forehead, and enlarged jaw and ears in most males and mild intellectual disability in many heterozygous females." *Dorland's* at 1830.

[21] A celiac screening shows tests for celiac disease, "an autoimmune malabsorption syndrome precipitated by ingestion of gluten-containing foods. It is characterized by inflammation of the small bowel mucosa; atrophy of intestinal villi with loss of their absorptive function; diarrhea and steatorrhea; abdominal distention; flatulence; weight loss; asthenia; deficiency of vitamins B, D, and K; and electrolyte depletion. Susceptibility is genetically determined and results from mutation at any of a number of gene loci." *Dorland's* at 530.

[22] Thyroid gland disorder is also called hypothyroidism and is defined as the "deficiency of thyroid activity, characterized by decrease in basal metabolic rate, fatigue, and lethargy; if untreated, it progresses to myxedema . . ." *Dorland's* at 907.

[23] Antinuclear antibody titer test revealed a 1:320 range in a diffuse pattern, which was positive under immunofluorescence. Pet'r's Ex. 10 at 2.

[24] An anti-Müllerian hormone titer is revealed from an anti-Müllerian hormone (AMH) test. "AMH is made in the reproductive tissues of both males and females . . . AMH plays an important role in the development of sex organs in an unborn baby." *Anti-Mullerian Hormone Test,* MEDLINEPLUS, https://medlineplus.gov/lab-tests/anti-mullerian-hormone-test/ (last visited Nov. 3, 2020).

[25] An erythrocyte sedimentation rate is "the rate at which erythrocytes precipitate out from a well-mixed specimen of venous blood, measured by the distance the top of the column of erythrocytes falls in a given

10 at 1–3; Pet'r's Ex. 8 at 4. Dr. Davis diagnosed Petitioner with ovarian failure and prescribed estrogen patches, levothyroxine,[26] and progesterone.[27] Pet'r's Ex. 8 at 4.

On March 26, 2014, Dr. Cook spoke with Petitioner's mother over the telephone about lab results. Pet'r's Ex. 11 at 7. The results included an elevated TSH level, which is suggestive of "sluggish thyroid function"; "reasonably good" free T4 and total T3 levels; negative anti-thyroglobulin antibody; [28] and a high TPO antibody count[29] that is "[consistent with] Hashimoto's thyroiditis." *Id.* On this call, Dr. Cook diagnosed Petitioner with chronic lymphocytic thyroiditis,[30] Hashimoto's thyroiditis, and POF. *Id.*

Petitioner returned to Dr. Gerba on March 27, 2014. Pet'r's Ex. 3 at 24–27. At this visit, Petitioner reported "occasional abdominal pain" and no menstrual period since December of 2013. *Id.* at 24. Dr. Gerba diagnosed Petitioner with POF and Hashimoto's thyroiditis. *Id.* at 25. Petitioner was told to continue taking progesterone and estradiol for her menopausal symptoms and to induce periods regularly. *Id.* at 25–26. Petitioner's lab work from this visit revealed elevated FSH, LH, and thyroid peroxidase antibodies; additionally, her TSH levels were low. *Id.* at 29–32.

On April 8, 2014, Petitioner presented to Jaya Srinivasan-Mehta, M.D., by referral from Dr. Gerba due to a March 13, 2014 positive ANA test. Pet'r's Ex. 13 at 3, ECF No. 15-2. Petitioner's physical exam was unremarkable. *Id.* at 3–4. Dr. Srinivasan-Mehta noted an overall "improvement of [Petitioner's] symptoms of hot flashes and mood swings since starting a hormone patch." *Id.* Dr. Srinivasan-Mehta's assessment was that Petitioner's ANA level was likely due to the Hashimoto's thyroiditis; and that the mildly positive double stranded DNA antibody test was

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time interval under specified conditions; an increase in rate is usually due to elevated levels of plasma proteins, especially fibrinogen and immunoglobulins, which decrease the zeta potential on erythrocytes by dielectric shielding and thus promote rouleau formation. It is increased in monoclonal gammopathy, hypergammaglobulinemia due to inflammatory disease, hyperfibrinogenemia, active inflammatory disease, and anemia." *Dorland's* at 1596.

[26] Levothyroxine, sometimes called levothyroxine sodium, or its brand-name Levoxyl, is a hormone "used as replacement therapy for hypothyroidism and in the prophylaxis and treatment of goiter and of thyroid carcinoma . . ." *Dorland's* at 1032.

[27] Progesterone is "the principal progestational hormone of the body, liberated by the corpus luteum, placenta, and in minute amounts by the adrenal cortex; it prepares the uterus for the reception and development of the fertilized oocyte by transforming the endometrium from the proliferative to the secretory stage and maintains an optimal intrauterine environment for sustaining pregnancy . . ." *Dorland's* at 1523.

[28] Thyroglobulin antibodies refers to "an iodine-containing glycoprotein of high molecular weight found in the colloid of thyroid gland follicles; it is made by thyroid follicular cells and secreted into the follicular lumen where it is iodinated, after which its iodinated tyrosyl moieties form the iodothyronines thyroxine and triiodothyronine. Thyroglobulins are then taken up by endocytosis into the follicular cells, where the iodothyronines are liberated by proteolysis, followed by release into the extracellular fluid and thence to the bloodstream." *Dorland's* at 1925.

[29] TPO refers to "thyroid peroxidase antibodies." A high TPO antibody count "can be a sign of: Hashimoto disease, also known as Hashimoto thyroiditis. This is an autoimmune disease and the most common cause of hypothyroidism . . ." *Thyroid Antibodies,* MEDLINEPLUS, https://medlineplus.gov/lab-tests/anti-mullerian-hormone-test/ (last visited Nov. 3, 2020).

[30] Chronic lymphocytic thyroiditis is another name for Hashimoto's disease. *See supra* note 3.

likely a false positive, because she had no signs or symptoms of lupus.[31] *Id.* at 5. Further, Dr. Srinivasan-Mehta noted that the positive ANA result "may be positive without any identifiable reason/disease in approximately 5-15% of the population," which "may occur secondary to polyclonal activation of the immune system following an infection, or it may be positive without any identifiable reason/disease." *Id.*

On April 24, 2014, Petitioner underwent an ultrasound, which confirmed her diagnosis of Hashimoto's thyroiditis. Pet'r's Ex. 9 at 1, ECF No. 7-9. On April 30, 2014, Petitioner presented to pediatric endocrinologist, Lynn Hawkins, M.D., for a second opinion on her diagnoses of POF and Hashimoto's thyroiditis. Pet'r's Ex. 8 at 4. At this visit, Petitioner reported having normal monthly menses up to December of 2013, but then developed hot flashes and an inability to concentrate. *Id.* All bloodwork, including thyroid, complete blood count, testosterone, FSH, LH, and estradiol levels were normal. *Id.* at 58–62. Petitioner's physical examination was normal. *Id.* at 56. Thyroid antibodies were not measured at this visit. *See id.* Petitioner's mother asked Dr. Hawkins if there was a connection between the HAV and ovarian failure; however, Dr. Hawkins did not record a response. *Id.* at 5. After reviewing Petitioner's medical history, Dr. Hawkins confirmed Petitioner's diagnosis of POF, goiter,[32] Hashimoto's thyroiditis, and palpitations.[33] *Id.* at 5–6. Dr. Hawkins recommended that Petitioner continue her medications and follow-up after additional lab work had been performed. *Id.*

Petitioner then presented to Beth Rackow, M.D., of the Center for Women's Reproductive Care for a pediatric gynecology consultation on May 1, 2014. Pet'r's Ex. 4 at 1–3, ECF No. 7-4. Dr. Rackow reviewed Petitioner's clinical history and lab results. *Id.* at 1. Dr. Rackow noted symptoms of hot flashes and absent menses that began in January of 2014. *Id*. Dr. Rackow did not offer a diagnosis or conduct a physical examination, at that time. *See id.*

On May 13, 2014, Dr. Gerba reduced Petitioner's estrogen dosage and temporarily stopped her progesterone in response to reported breast pain and lower abdominal pain. Pet'r's Ex. 3 at 22–23; Pet'r's Ex. 8 at 9. A week later, on May 22, 2014, Dr. Hawkins spoke with Petitioner's mother by telephone. Pet'r's Ex. 8 at 9. Petitioner's mother requested to check whether Petitioner received the correct vaccine on July 16, 2013, because she wanted to make sure Petitioner received HAV, and not HPV by mistake. *Id.* Results showed that Petitioner received the Hepatitis A vaccine. *Id.* at 8.

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[31] Lupus is sometimes referred to as "systemic lupus erythematosus." *Dorland's* at 1079. It is defined as "a chronic, inflammatory, often febrile multisystemic disorder of connective tissue that proceeds through remissions and relapses; it may be either acute or insidious in onset and is characterized principally by involvement of the skin, [] joints, kidneys, and serosal membranes. The etiology is unknown, but it may be a failure of regulatory mechanisms of the autoimmune system, since there are high levels of numerous autoantibodies against nuclear and cytoplasmic cellular components. The condition is marked by a wide variety of abnormalities, including arthritis, arthralgias, nephritis, central nervous system manifestations, pleurisy, pericarditis, leukopenia or thrombocytopenia, hemolytic anemia, an elevated erythrocyte sedimentation rate, and the presence in the blood of distinctive cells called LE cells." *Id.*

[32] Goiter is defined as "an enlargement of the thyroid gland, causing a swelling in the front part of the neck." *Dorland's* at 796.

[33] A palpitation is "a subjective sensation of an unduly rapid or irregular heartbeat." *Dorland's* at 1365.

On June 26, 2014, Dr. Rackow noted concern that Petitioner was on "too low" a dose of estrogen-progestin regimen. Pet'r's Ex. 15 at 6, ECF No. 20-1. Dr. Rackow wrote that "[Petitioner] may have had side effects due to immediate start at high doses. [I w]ill taper up each month back to full dose." *Id.* On the same day, Dr. Gerba started Petitioner on progesterone again. Pet'r's Ex. 8 at 21.

Petitioner returned to Dr. Gerba on July 14, 2014, where he diagnosed Petitioner with scoliosis[34] and depression. Pet'r's Ex. 3 at 11–12. Petitioner had an additional hormone study performed, which showed thyroid function and gonadal function had normalized under the hormone replacement therapies. *Id.* at 14. On October 9, 2014, Dr. Gerba stated that Petitioner is in good physical health and able to participate fully in physical activities. *Id.* at 3.

On February 23, 2015, Petitioner returned to Dr. Rackow for a follow-up visit. Pet'r's Ex. 15 at 2; Pet'r's Ex. 111 at 1–2, ECF No. 81-1. Dr. Rackow wrote that Petitioner was "overall doing well" with five-day menses and minimal side effects since using MPA. Pet'r's Ex. 15 at 2. She noted concerns that Petitioner is infertile and continued to be treated for ovarian insufficiency and Hashimoto's thyroiditis. *Id.*

Petitioner presented to Dr. Hawkins for a follow-up on an endocrine test concerning Hashimoto's thyroiditis and POF on June 10, 2015. Pet'r's Ex. 120, ECF No. 88-4. The lab work that was taken on May 15, 2015, showed normal hormone and TFT values. *Id.* at 1. Petitioner reported that her hypothyroidism is "doing well and [she is] without complaints." *Id.* The physical examination at this visit was unremarkable. Dr. Hawkins adjusted Petitioner's medication and asked her to return in a year. *Id.* at 2.

On March 10, 2016, Petitioner presented to Charles Grant, M.D., a Precision and Alternative Medicine Physician, for a second opinion. Pet'r's Ex. 91, ECF No. 57-1; Pet'r's Ex. 115 at 41–48, ECF No. 81-5; Pet'r's Ex. 118 at 1. He wrote in a letter that it was his "opinion that [Petitioner's] present condition was caused by the Hep[.] A vaccination." Pet'r's Ex. 91 at 1. Dr. Grant started Petitioner on supplements and natural remedies to treat the autoimmune disease. Pet'r's Ex. 115 at 9. He also transitioned Petitioner from Provera[35] to progesterone cream because Petitioner's parents were concerned about the potential carcinogenic effects of Provera. Pet'r's Ex. 118 at 1. Prior to Dr. Grant's assessment that HAV attributed to Petitioner's diseases, a temporal relationship was mentioned in Petitioner's medical history but never causally linked.

Petitioner presented to Patricia Vaguin, M.D., for another opinion on the diagnosis of POF and autoimmune Hashimoto's thyroiditis on July 13, 2016. Pet'r's Ex. 121 at 1, ECF No. 88-5. In the medical history section, Dr. Vaguin noted that Petitioner's symptoms began a few weeks after her July 2013 vaccination. *Id.* Dr. Vaguin confirmed the diagnoses, recommended that Petitioner focus on psychosocial support, and recommended that Petitioner continue with her current

[34] Scoliosis is defined as "an appreciable lateral deviation in the normally straight vertical line of the spine." *Dorland's* at 1681.

[35] Provera is the brand-name for medroxyprogesterone acetate and is defined as "a progestin administered orally for treatment of secondary amenorrhea and dysfunctional uterine bleeding, induction of menses, prevention and treatment of endometrial hyperplasia in postmenopausal hormone replacement therapy, and testing for endogenous estrogen production . . ." *Dorland's* at 1120.

treatment plan. *Id.* at 3. The remaining medical records indicate that Petitioner continues to be evaluated and treated for POF and Hashimoto's thyroiditis. *See* Pet'r's Exs. 118–122; 124–127, ECF Nos. 88, 106, 108, 109.

b. Candie Decker's Statement and Testimony

Petitioner's mother, Candie Decker, filed an affidavit along with the Petition. *See* Pet'r's Ex. 1. In her affidavit, Ms. Decker attested that Petitioner had been a "healthy and fit girl without any medical problems" before the vaccination. *Id.* ¶ 2. Additionally, Ms. Decker wrote that Petitioner's menstrual cycle began at the age of eleven, and "it was always very regular and normal." *Id.* ¶ 3.

Ms. Decker wrote that on July 16, 2013, Petitioner received the HAV at the age of thirteen, and "[Petitioner's] menstrual cycle became abnormal and irregular" within a month of receiving the vaccination. *Id.* ¶¶ 1, 4. Ms. Decker alleged that Petitioner stopped menstruating after December of 2013, and subsequent blood work showed high FSH levels and low estrogen levels. *Id.* ¶ 8. Ms. Decker wrote that, as a result of the blood work, Petitioner was diagnosed with amenorrhea on February 17, 2014, POF on February 25, 2014, and Hashimoto's thyroiditis on March 27, 2014. *Id.* ¶¶ 8–10.

Ms. Decker attested that Petitioner continues to "visit doctors and specialists in an effort to get a handle on her condition," and her symptoms have not remitted. *Id.* ¶¶ 14, 17. Ms. Decker wrote that Petitioner "takes estrogen patches twice a week, levothyroxine daily, and has to take progesterone monthly to bring on a period and keep her uterus healthy." *Id.* ¶ 15. Additionally, Ms. Decker stated that "[Petitioner's] ability to function in society is severely impaired due to the symptoms she suffered and psychological effects from the reality of infertility[.]" *Id.* ¶ 16.

During the hearing, Ms. Decker provided an account of the chronology of Petitioner's symptoms that was consistent with her written statement and medical records. Tr. 22–26. She also described Petitioner's new day-to-day and the emotional toll that this condition has had on her daughter, as far as she can see. Tr. 27–29. Ms. Decker testified that she has "tried to keep [Petitioner's] life as normal as possible," Tr. 29:9–10, and they "don't dwell on the infertility," Tr. 29:16. The goal for Petitioner's mother is to keep her healthy, and she hopes her daughter doesn't develop any additional autoimmune diseases. Tr. 29:17–18. Ms. Decker described the entire ordeal as "heartbreaking." Tr. 29:25.

c. Petitioner's Written Statement and Testimony

Petitioner submitted a statement prior to testifying at the hearing. *See* Pet'r's Ex. 123, ECF No. 106-1. The statement was intended to be in lieu of testifying, but Petitioner ultimately testified on the first day of the hearing. In her statement, Petitioner stated that at age thirteen, she "was persuaded by [her] doctor to get a Hepatitis A vaccine to prevent [her] from getting sick on [a cruise]." *Id.* at 1.

Petitioner wrote that "[she] started noticing changes in [her] body" shortly after she began her freshman year of high school. *Id.* Petitioner conveyed that "the most significant and most

traumatizing" of the changes were the hot flashes, which made it impossible to focus on any task and difficult to fulfill her responsibilities. *Id.* In addition to the hot flashes, Petitioner also began missing her periods. *Id.* Petitioner stated that she had always been healthy and questioned the timing of the disease symptoms in relation to HAV as not coincidental. *Id.*

Petitioner had to travel and miss school to receive a diagnosis, which was both expensive and taxing on her physically and emotionally. *Id.* at 2. Petitioner stated that she was diagnosed with POF, which produced an autoimmune "chain reaction within [her] body," resulting in "Hashimoto's disease, or hypothyroidism, and . . . goiter." *Id.* The medications Petitioner took to control the symptoms "came with side effects, such as abdominal pain, breast pain, dizziness, and extreme heavy bleeding." *Id.* Petitioner wrote that her regimen of medication and specialists has been hard to maintain along with "college, [two] jobs, sorority, friends, and family." *Id.* Additionally, Petitioner lamented over her fertility complications. *Id.* at 3.

When she was asked about traveling to Washington, D.C. to attend the hearing, Petitioner did not "think that [she could] physically or emotionally do it." *Id.* Petitioner stated that she did not "fully understand why [she] need[ed] to go to Court to convince people that [her] life was turned upside down after [she] got the vaccine in 2013." *Id.* Also, she did not "think that [she] could handle listening to people telling [her] about [her] own body and that what happened to [her] was just a coincidence," or reminded of her injuries again. *Id.* Further, Petitioner did not want to hear any speculation as to potential diseases that she may develop later in life. *Id.*

Petitioner testified via telephone at the hearing. Tr. 60:3–74:14. She indicated that she began her menstrual cycle "a couple years before the incident" when she was approximately eleven years of age. Tr. 61:7–8. When her cycle started, according to Petitioner, "it was very regular." Tr. 61:22–23. She testified that she did not have any irregular bleeding, and it the timing was predictable. Tr. 61:23–24. The first sign that Petitioner remembered indicating there was a problem was when she had two periods in one month. Tr. 62:10–11. At that time, she was reassured by both her doctor and negative test results that it was likely a coincidence. Tr. 62:13–15.

All the symptoms that followed Petitioner's irregular cycle occurred shortly thereafter, and she was ultimately diagnosed with POI in February of 2014. Tr. 63:3–4, 64:21–24. I asked Petitioner about her hypothyroidism, and she remembered she had a swollen neck right before that diagnosis. Tr. 71:5–6. Petitioner testified that she "didn't know which symptoms went with which diagnosis, but [she knew] definitely the goiter and the hormones were the — were the hypothyroidism." Tr. 71:11–13. Although diagnosed at two different times, Petitioner described the symptoms as "like it was all coming on at once." Tr. 71:24. She was "not really sure if it was a progression [of continuous symptoms] or not." Tr. 71:25.

III. Experts

a. Expert Qualifications

i. Petitioner's Expert, Dr. James M. Wheeler

Dr. Wheeler wrote two expert reports in this case and testified in the hearing. *See* Pet'r's Exs. 16, 31; Tr. 34:11–57:14, 74:16–125:5, 557:7–570:21. Dr. Wheeler completed his medical degree and residency at Baylor University. Pet'r's Ex. 16 at 1; Pet'r's Ex. 17, Dr. Wheeler's CV ("Wheeler CV") at 1, ECF No. 23-2. He also completed specialty fellowships at Yale in medical endocrinology; reproductive endocrinology and infertility; and clinical epidemiology and health policy. Wheeler CV at 1–2. Additionally, Dr. Wheeler earned a Juris Doctorate at the University of Houston. *Id.* Dr. Wheeler is board certified in obstetrics and gynecology. Tr. 36:22–25. He served as an assistant professor from 1988 to 1996. Wheeler CV at 1. Since 1994, Dr. Wheeler has been in private practice as a reproductive endocrinologist and an obstetrician/gynecologist. *Id*. He has authored or co-authored over fifty articles, two books, and twenty-five chapters in medical texts, many of them focusing on fertility and endometriosis. *Id.* At the hearing, Petitioner moved to have Dr. Wheeler entered as an expert in obstetrics and gynecology as well as reproductive endocrinology. Tr. 46:9–11. Respondent objected to Dr. Wheeler being qualified as an expert in reproductive endocrinology because he was not board certified in that area. Tr. 46:15–47:12. Due to his clinical experience, I qualified him to testify as an expert in obstetrics and gynecology, and reproductive endocrinology over objection. Tr. 47:16–50:17.

ii. Petitioner's Expert, Dr. Yehuda Shoenfeld

Dr. Shoenfeld offered an expert report in this case and testified at the hearing. Pet'r's Ex. 50; Tr. 228:20–305:14. In 1972, Dr. Shoenfeld received his medical degree from the Hebrew University's Hadassa Medical School in Israel. Pet'r's Ex. 51, Dr. Shoenfeld's CV ("Shoenfeld CV") at 2, ECF No. 43-2. He is an emeritus Professor at the Tel–Aviv University Medical School, Sackler Faculty of Medicine, and served as the head of the Department of Medicine at the Sheba Medical Center of Tel–Aviv University, the largest hospital in Israel. Shoenfeld CV at 4; Tr. 229:10–231:12. He also has served as the head of the Hybridoma Unit and Research Laboratory for Autoimmune Diseases of the Soroku Medical Center of Ben–Gurion University of the Negev, and, in that capacity, he founded the Center for Autoimmune Diseases, where he serves as Director. Shoenfeld CV at 2. Dr. Shoenfeld has authored or co-authored over one-thousand-eight-hundred articles, fifty books, and one-hundred-and-forty chapters in medical texts, many of them focusing on autoimmune diseases. *See generally* Shoenfeld CV; Pet'r's Ex. 50 at 1. He is the Editor–in–Chief of Autoimmunity Reviews, is a Co–Editor of the Journal of Autoimmunity, and has served on the Editorial Boards of numerous other medical journals. *See* Shoenfeld CV; Tr. 230:21–231:6. At the hearing, I qualified Dr. Shoenfeld to testify as an expert in immunology and autoimmunology. Tr. 238:5–9.

iii. Petitioner's Expert, Dr. Steven Pike

Dr. Steven Pike offered an expert report in this case and testified at the hearing. *See* Pet'r's Ex. 92; Tr. 125:17–226:10. Dr. Pike received his medical degree from the University of New

Mexico and completed his residency at the University of Arizona. Pet'r's Ex. 93, Dr. Steven Pike's CV ("Pike CV") at 1, ECF No. 71-2; Tr. 126:14–127:6. He is board-certified in toxicology, emergency medicine, occupational and environmental medicine, and industrial hygiene. Tr. 128:2–9. Dr. Pike primarily practices as an emergency physician and a medical toxicologist in New Mexico. Tr. 126:2–6. At the hearing, I qualified Dr. Pike to testify as an expert in medical toxicology. Tr. 134:24–135:2.

iv. Respondent's Expert, Dr. Patrizio Caturegli

Dr. Caturegli filed two expert reports and testified at the hearing. Resp't's Exs. A, E; Tr. 393:11–449:11. In 1987, Dr. Caturgeli received his medical degree from the University of Pisa in Italy. Resp't's Ex. B, Dr. Caturegli's CV (Caturegli CV) at 1, ECF No. 30-2; Tr. 394:13–14. He completed his residency at the University of Pisa in endocrinology, a subsequent fellowship at Johns Hopkins University in immunology, and a second residency at Johns Hopkins in pathology. Caturegli CV at 1; Tr. 394:13–21.

Since 1999, Dr. Caturegli has been an educator of immunopathology at Johns Hopkins. Caturegli CV at 2; Tr. 393:23–25. He also directs the division of immunology and the clinical immunology laboratory in the department of pathology at Johns Hopkins. Tr. 394:2–7. He has over one hundred publications, ten book chapters, and has given many talks on thyroid disease. Caturegli CV at 3–10, 13, 18–19. Dr. Caturegli is board certified in endocrinology from the Italian Board of Endocrinology and clinical pathology from the American Board of Pathology. Caturegli CV at 16; Tr. 394:23–25. At the hearing, I qualified Dr. Caturegli to testify as an expert in immunology and endocrinology. Tr. 396:15–20.

v. Respondent's Expert, Dr. David Frankfurter

Dr. Frankfurter offered one expert report and testified at the hearing. Resp't's Ex. C; Tr. 308:19–449:11, 571:23–582:12. He earned his medical degree from Yale University. Resp't's Ex. D, David Frankfurter's CV ("Frankfurter CV") at 1, ECF No. 30-4; Tr. 309:17–18. Dr. Frankfurter completed a residency in obstetrics and gynecology at Yale and a fellowship in reproductive endocrinology at Harvard University. Frankfurter CV at 1; Tr. 309:19–22.

Dr. Frankfurter is board certified in general obstetrics/gynecology and reproductive endocrinology. Frankfurter CV at 2; Tr. 310:2–3. He is currently the Division Director of Reproductive Endocrinology, Fertility, and IVF and a Professor of Obstetrics and Gynecology at The George Washington University. Frankfurter CV at 3–4; Tr. 309:6–10. Dr. Frankfurter has covered reproductive endocrinology and POF through his fifty published articles and abstracts, three book chapters, and eleven lecture series. Frankfurter CV at 6–16. At the hearing, I qualified Dr. Frankfurter to testify as an expert in obstetrics and gynecology with a subspecialty in reproductive endocrinology and fertility. Tr. 312:2–9.

vi. Respondent's Expert, Dr. Edward Cetaruk

Dr. Cetaruk submitted two expert reports, submitted a whitepaper detailing adjuvants, and testified at the hearing. Resp't's Exs. F, H, I; Tr. 456:11–549. He received his medical degree at

New York University School of Medicine, in 1991. Resp't's Ex. G, Dr. Edward Walter Cetaruk's CV ("Cetaruk CV") at 2, ECF No. 64-6; Tr. 456:25–457:1. From 1991 to 1994, he completed a residency in Emergency Medicine at the University of Massachusetts Medical Center. Cetaruk CV at 2–3; Tr. 457:1–3. From 1994 to 1996, he completed concurrent fellowships in Emergency Medicine Research at the University of Colorado Health Sciences Center and in Medical Toxicology at the Rocky Mountain Poison Center in Denver. Cetaruk CV at 2–3; Tr. 457:3–7.

Over the course of his career, Dr. Cetaruk has received board certifications from the American College of Toxicology, the American Board of Emergency Medicine (with special qualifications in Medical Toxicology), and the National Board of Medical Examiners. Cetaruk CV at 1; Tr. 457:11–14. His CV lists numerous medical articles and book chapters that he has authored or co-authored. Cetaruk CV at 9–11. He has been invited to present lectures at dozens of medical conferences and medical schools in the United States and internationally. *Id.* at 8–9.

Dr. Cetaruk practices emergency medicine within the University of Colorado Health System and practices toxicology within his own practice. Cetaruk CV at 3–5; Tr. 457:16–23. He also teaches toxicology at the University of Colorado. Cetaruk CV at 2; Tr. 457:24–458:3. At the hearing, I qualified Dr. Cetaruk to testify as an expert in toxicology and emergency medicine without objection. Tr. 461:22, 462:24–2.

b. Expert Reports and Testimony

i. Dr. Wheeler (Petitioner)

In his initial report, Dr. Wheeler began with the premise that "[v]accinations can cause an autoimmune reaction." Pet'r's Ex. 16 at 5. He noted that "albeit imperfect" due to testing issues and incidence rarity, medical literature does provide a "solid medical theory that . . . Hep[.] A vaccine[] could cause autoimmune disease." *Id.* In support, Dr. Wheeler testified that the Karali et al. article[36] identified children who were immunized with HAV and later developed ANA markers. Tr. 97:23–25, 98:1–2. He opined that experts in favor of vaccination "propose overly strict criteria," including consistency and strength "across different patient cohorts," specificity of vaccine and symptoms, temporal relation, consistent results "using different methodology," and prevalence variances "between the vaccinated population vs. non-vaccinated control population," to establish a causal relationship between rare adverse events and vaccinations. *Id.* He concluded that this level of proof is untenable and that "there is sufficient evidence . . . that Hep[.] A vaccine can indeed induce autoantibodies, and therefore in a subset of those patients developing autoantibodies, actually symptomatic autoimmune disease." *Id.*

Dr. Wheeler continued in his first report with a discussion of POF. Pet'r's Ex. 16 at 7. He noted that the condition is extremely rare in teenagers and difficult to diagnose because "the criteria for defining POF are not always standard." *Id.* A definitive diagnosis, Dr. Wheeler noted, is based on three criteria, "amenorrhea for 3–6 months, the demonstration of FSHA concentrations above 40 mIU/ml on at least two occasions . . . and low estrogen (sic) levels." *Id.* He also identified

[36] Citing Pet'r's Ex. 23, ECF No. 25-5, Karali, Z., et al., *Autoimmunity and Hepatitis A Vaccine in Children,* 21:5 J. INVESTIG. ALLERGOL. CLIN. IMMUNOL. 389, 389–393 (2011).

several known causes of POF, including "[a]utoimmune disease, estimated to comprise up to 30% of POF cases." *Id.* at 7–8.

While there is an association between POF and anti-ovarian antibodies, Dr. Wheeler acknowledged that they are not found consistently or exclusively in POF patients. *Id.* at 8. He noted that approximately "10–20% of women with POF will have organ-specific antibodies especially to the thyroid or adrenal glands" and identified thyroiditis as "the most frequent autoimmune disorder associated with POF." *Id.* Ultimately, Dr. Wheeler wrote that "[t]he exact link between POF and autoimmune (sic) is unclear." *Id.*

Dr. Wheeler wrote that he needed to, in the "simplest" terms, establish "that the alleged vaccine was actually given[,]" and "that the alleged disease actually followed the vaccination." *Id.* Acknowledging that a temporal relationship is not sufficient on its own to establish causation, Dr. Wheeler stated that "in the absence of other known causes and the presence of strong evidence of autoimmunity, then an autoimmune cause becomes the most probable." *Id.* at 9. In support of his opinion that vaccine-induced injury occurred in this case, Dr. Wheeler listed the following as evidence: "A.D. has no evidence of autoimmune disease, and thus no particular vulnerability . . . , A.D. had normal pubertal milestones up until [vaccination and,] A.D. lacks a history of other known causes of POF . . .[,]" including genetic causes. *Id.* at 10.

According to Dr. Wheeler, "[Petitioner]'s story best fits an abbreviated menopause, a normal six to eight-year process that has been compressed into a matter of a few months." Tr. 76:6–8. He argued that "[i]t would take an entire egg cycle of 2 ½ months for the oocytes[37] to be sufficiently hurt to become hormonally menopausal." Tr. 107:1–3. Dr. Wheeler testified that her presentation was "more akin to something poisoning the ovaries" than something acutely traumatic, such as surgery. Tr. 76:9–10. He discussed the proteinuria that pre-existed A.D.'s vaccination, but testified that "if [it] continued, if it worsened, we would have evaluated her for autoimmune disease." Tr. 81:2–4.

In a responsive report, Dr. Wheeler acknowledged that "A.D.'s family history for autoimmune disease . . . certainly put her at risk for the autoimmune thyroiditis and POF she later experienced. Pet'r's Ex. 31 at 3. He testified that despite A.D.'s family history, her treaters ruled out any chromosomal cause of her conditions. Tr. 94:6–7. Dr. Wheeler then opined that A.D.'s enlarged goiter was a sign of autoimmunity. Tr. 94:9–10. He continued that the pattern of A.D.'s enlarged goiter pointed to a "diffuse autoimmune response as compared to some patterns that go with more specific diseases." Tr. 95:2–4. Dr. Wheeler wrote that "[v]accines are specifically designed to mimic the antigenicity of infections; thus, if infections precede autoimmune diseases, then certainly antigenically-similar vaccines could as well." Pet'r's Ex. 31 at 4. Dr. Wheeler reframed any argument that there is a lack of scientific evidence linking HAV to POI, writing that "more accurate wording would be 'not copious' and 'not fully developed' scientific evidence." *Id.* at 6. When asked directly to identify the likely mechanism of A.D.'s POI, Dr. Wheeler discussed bystander activation and molecular mimicry. He wrote that "no expert can definitely know, or prove, what caused A.D. (sic) autoimmune disease, [but] this is certainly the most plausible one . . ." *Id.* at 15–16.

[37] An oocyte is "the immature female reproductive cell prior to fertilization, derived from an oogonium and occurring in two stages, primary and secondary oocytes." *Dorland's* at 1322.

Dr. Wheeler described the variability of autoimmune pathogenesis. He testified that "[l]atencies can be as short as ten days . . . and then latencies to disease can be as long as years, like in type I diabetes and lupus." Tr. 121:22–24. Assuming that no one disputed the autoimmune nature of A.D.'s POI, Dr. Wheeler testified that other than her HAV, "I don't have any other factor on my differential diagnosis." Tr. 123:8–9. Dr. Wheeler testified that if he were asked "does this woman's familial susceptibility put her at risk for autoimmune disease her entire life, I would say yes." Tr. 124:15–17. POF, however, is just too rare at "less than one in a million," to be completely a result of heredity. Tr. 124:24.

On recall, Dr. Wheeler testified that he was not concerned about the overall size of either of Petitioner's ovaries, or the discrepancy in size between the two. Tr. 562:2–4. He noted that ultrasounds are imprecise and stated that he "[doesn't] think [the study of Petitioner's ovaries] indicates either a short[]standing or longstanding disease." Tr. 562:15–16. Dr. Wheeler did assert, however, that a MCM8 mutation "is a common denominator of the vast majority of chromosomal and genetic disorders that cause POF." Tr. 564:2–4. He continued that MCM8 dysfunction would cause Petitioner to "experience ovarian failure and associated symptoms thereof. This would be an example of an acquired MCM8 genetic POF, acquired genetic very often called autoimmunity." Tr. 564:20–23. When asked if he had any evidence that MCM8 protein was expressed in the ovaries post-puberty, Dr. Wheeler admitted that he had "not researched that," and did not have it. Tr. 565:6–7. Dr. Wheeler did not deny that Petitioner could have developed any number of autoimmune diseases later in life directed at any number of organs. Tr. 566:4–5. In fact, had Petitioner developed this condition later in life, Dr. Wheeler testified that this case "would be more like the [non-vaccine induced] POIs [they have] been talking about." Tr. 566:10–11. This case is different, in his opinion, because "she received this vaccine, and with the life cycle of her eggs, she developed a profound and deeply severe ovarian failure." Tr. 566:6–8.

ii. Dr. Yehuda Shoenfeld (Petitioner)

Dr. Shoenfeld identified three "logical medically plausible combined mechanisms of molecular mimicry, adjuvant induced autoimmunity and direct aluminum toxicity, leading to the development of [POI] and autoimmune thyroiditis following [HAV]." Pet'r's Ex. 50. His written expert report consisted of a detailed explanation of these various mechanisms, beginning with molecular mimicry. *See id.* Dr. Shoenfeld discussed case studies of POF following HPV, noting that in all four cases, there was a clear temporal relationship and no other identified possible causes. *Id.* at 6. From there, Dr. Shoenfeld sought to identify potential protein chains for cross-reaction. *Id.* Ultimately, he found that "[t]here is a molecular identity represented by the hexapeptide REAGRI, which is common to [HAV] and the human DNA helicase MCM8." *Id.* Dr. Wheeler and Dr. Shoenfeld both noted that MCM8 is integral in ovarian function. Dr. Shoenfeld concluded that "molecular mimicry [is] a plausible mechanism for the POF developed in A.D.'s case following [HAV]." *Id.* at 7.

Aluminum adjuvant induced autoimmunity ("ASIA") is the second mechanism that Dr. Shoenfeld discussed. *Id.* at 8. He noted that adjuvants, or "substance[s] that act[] to accelerate, prolong or enhance antigen-specific immune response" are present in every Hepatitis A vaccine. *Id.* He continued, this response can lead to autoimmunity, and Dr. Shoenfeld mentioned other "similar infectious mechanisms" such as "epitope spreading, bystander activation[,] and

polyclonal activation." *Id.* In the present case, Dr. Shoenfeld wrote that "the state of hyper-activation of the immune system created by the adjuvant-associated HAV[] given to AD, would create an autoimmune response against the ovary, leading to the development of POF." *Id.*

Lastly, Dr. Shoenfeld discussed direct aluminum toxicity as a mechanism. *Id.* at 8–9. Citing animal studies, he wrote that "testosterone, FSH, and LH were significantly reduced in Al-treated rats." *Id.* at 9. Dr. Shoenfeld argued that other studies are consistent in their findings, including a study that "demonstrated inhibition of reproductive functions in female rats during sub-chronic aluminum exposure in drinking water[,]"[38] and that aluminum "hampered body weight" and "suppressed secretions of estradiol [and] progesterone."[39] *Id.* at 9.

All three of these mechanisms, in Dr. Shoenfeld's opinion, developed as a result of the HAV, and together, they caused A.D.'s POF. *Id.*

Dr. Shoenfeld began his testimony by restating the basis for his opinion that Petitioner's POI was vaccine induced. He testified: "[p]oint number one is that there is no evidence whatsoever and no hints in [Petitioner's background] that she was sick or she had anything to predict that she would develop autoimmune [POI] except of the fact that she had a genetic preponderance." Tr. 244:13–17. He continued with point number two: "the appearance of the symptoms . . . to the time that she was diagnosed with autoimmune [POI] ranges between three weeks, one month to two months, which is usually the timeframe, that is asked, demanded by the court." Tr. 245:4–9.

Dr. Shoenfeld then described how molecular mimicry occurs within this timeframe using the example of rheumatic fever following a streptococcus bacterial infection. Tr. 247:12–15. Streptococcus has a polypeptide chain that is similar in structure to a polypeptide chain found in human heart valves, the brain, and our joints. Tr. 248:2–5. When the bacteria enters the human body, our immune system produces antibodies to fight it that can be "misled by the similarity in the structure of the [peptide chains naturally present in these organs]." Tr. 248:10–13. Dr. Shoenfeld explained that although it can take three weeks for symptoms to develop, "[s]ometimes we don't know, the patient didn't realize that she or he had the infection," because the symptoms were mild." Tr. 249:6–8. Sometimes, according to Dr. Shoenfeld, in the case of cross-reactivity with the heart, "when a woman is grown up . . . and subjected to [examination,] they reveal the deformed valves years after the streptococcus invaded the body." Tr. 249:12–15. The difference, Dr. Shoenfeld opined, "between the first symptom and the eventual diagnosis of a disease as an autoimmune disease," Tr. 250:1–3, is varied; "because it takes time between the binding of the autoantibody to the organ and the eventual development of enough damage to the organ to be represented[.]" Tr. 250:4–7.

Dr. Shoenfeld applied this analogy to Petitioner's case. He opined that "the timing of the tragic event that happened to [Petitioner] is exactly what the Court has required for a cause-and-effect relationship between environmental factor and development of, in this case, autoimmune disease." Tr. 250:12–16. Based on his understanding of the Court's standard, Dr. Shoenfeld did

[38] Citing Pet'r's Ex. 82, ECF No. 98-4, Fu, Y., et al., *Effects of sub-chronic aluminum chloride exposure on rat ovaries,* 100:1 LIFE SCIENCES 1, 1–6 (2014).
[39] Citing Pet'r's Ex. 83, ECF No. 98-5, Wang, N., et al., *Effects of subchronic aluminum exposure on the reproductive function in female rats,* 145:3 BIOL. TRACE ELEMENT RESEARCH 382, 382–87 (2012).

not believe that an actual cause-and-effect relationship was necessary, "because if [present, the vaccine-induced condition] will be in the table of the Vaccine Court." Tr. 250:20–23. Instead, he asserted that a plausible mechanism is necessary, which he likened to "logical." Tr. 18–20.

Continuing with his discussion regarding molecular mimicry, Dr. Shoenfeld testified that the medical literature filed in this case established that Hepatitis A can cause the development of autoantibodies. Tr. 6–11. Specifically, Dr. Shoenfeld identified gammaglobulin[40] and noted that humans will increase production following "stimulat[ion] from outside, either by the virus or by an adjuvant or by anything in the environment." Tr. 253:17–19. He then highlighted the role of "the ingredient of the virus in the vaccine, which is emulsified with the adjuvant, in this case aluminum." Tr. 253:23–25. In this case, Dr. Shoenfeld explained, where molecular mimicry occurred, is that one constituent in the vaccine Petitioner received contained a peptide that also "appears on an important functional constituent of the ovary which is an enzyme, an active ingredient of the metabolism and different reaction which is responsible for protecting the ovary and enabling the ovary to have mature oocytes." Tr. 254:14–18. He concluded that cross-reactivity occurred, and Petitioner was then unable to develop mature oocytes. Tr. 254:20–25. Cross-reactivity can result in the inactivation of the enzyme. This can occur if the enzyme is killed (or blinded) or blocked. Tr. 255:19–20, 256:2. Dr. Shoenfeld stressed that in this case, molecular mimicry was "enhanced by the other two points, the toxic effect of aluminum and the enhancement of the immune system." Tr. 256:14–16.

Although the relevant peptide chain only contained six amino acids, Dr. Shoenfeld asserted that "if you inject even five amino acid (sic) with an adjuvant, it will not happen without an adjuvant, you will raise an immune system which will be specifically recognizing this sequence and therefore will specifically organize the ovary." Tr. 6–10. In this case, the adjuvant is aluminum, and although he is not a toxicologist, Dr. Shoenfeld testified that he has reviewed medical literature that discusses the deleterious effects of aluminum adjuvant on the ovaries of several animal species, including humans. Tr. 258:21–25, 259:1–11. When injected, Dr. Shoenfeld explained, "aluminum is absorbed very quickly to the circulation." Tr. 259:21–22. He contrasted this type of absorption with ingestion, noting "once in the circulation, in several minutes, it will come to all of our organs in the body." Tr. 259:25, 260:1. This is because "the tissue construction of the ovary is such that it absorb[s] the aluminum from the circulation." Tr. 260:2–4. Dr. Shoenfeld testified that other organs may be affected, such as the thyroid, which was also affected by autoimmune disease in Petitioner's case. Tr. 260:5–7.

To support his conclusion that "aluminum is toxic to our body," Dr. Shoenfeld discussed a patient suffering from chronic renal failure. After receiving dialysis, this patient, along with others, developed encephalopathy. Tr. 260:12–14. Dr. Shoenfeld explained that aluminum was found in the dialysis, and no additional encephalopathy developed in patients after the aluminum was removed from the dialysis. Tr. 260:19–21. He went a step further and noted that not only is aluminum toxic, because it is a heavy metal, it is also "known to induce autoimmune disease." Tr. 261:11–12. Despite these concerns with aluminum, it has been used extensively in vaccines because it "is extremely important to enhance the reaction, the immune reaction." Tr. 263:24–25.

[40] Gammaglobulin is also called immunoglobulin and is defined generally as "any of the structurally related glycoproteins that function as antibodies . . . divided into five classes . . . on the basis of structure and biological activity." *Dorland's* at 919.

Dr. Shoenfeld asserted that "[t]he reason why the vaccine companies include the aluminum and actually adjuvant [in inactive vaccines] is because they are not immunogenic." Tr. 262:13–15. He explained, "adjuvant comes from the Latin word, adjuvare – to help." Tr. 264:1–2. If Petitioner had "been subjected to just the vaccine without the aluminum adjuvant, it might be that she would not be — she would not develop the autoimmune disease of the ovary." Tr. 264:2–6. Dr. Shoenfeld testified that all three mechanisms he discussed were working in tandem but noted the importance of the adjuvant. Even in cases that don't involve the same vaccine Petitioner received, the presence of the aluminum adjuvant may be enough to produce the same result. He drew an analogy to Hepatitis A: "[w]e have the adjuvant to enhance the immune system and we have both in HPV molecular mimicry . . . and also in this case the peptide and the enzyme on the chromosome which are directing the sensitivity to the ovary." Tr. 265:6–11.

Asked about the lack of studies to support his conclusions, Dr. Shoenfeld asserted that "[i]t's almost impossible . . . to do these studies." Tr. 265:19–20. Furthermore, "young women tend today to take contraceptives, and they tend to take it quite early. And this is the time when they get the vaccines." Tr. 265:24–25, 266:1–2. He reasoned that, "even if [a young woman were to] develop the autoimmune ovarian failure, the symptoms are masked completely because this is a therapy to diminish or eliminate the symptom, they take the contraceptives." Tr. 266:2–5. By "the age of 30 or maybe 28 they would like to become pregnant, [but] they can't. And then many of the gynecologist or reproductive immunology will say it's idiopathic because they cannot relate it to the vaccine that destroyed the ovaries years ago." Tr. 266:6–12.

Dr. Shoenfeld then discussed a paper by Gail DeLong,[41] that concluded there was a lower probability of pregnancy in females in the U.S. if they received the HPV vaccine. Tr. 266:17–19. He noted that "if you will read the abstract, you will get to the lower number of infertile females which increased only since the time of the introduction of the papillomavirus to the market in the USA." Tr. 267:10–13. When pressed about his assertion that DeLong identified an increase in infertility, Dr. Shoenfeld was asked if the study included any information that indicated these women had abnormal menstrual cycles. He admitted that he did not know but also stated that infertile women are not healthy. Tr. 296:10–12. Dr. Shoenfeld testified, "[t]his is poor quality when a woman cannot give birth." Tr. 296:15. The study found that the women in the study had not given birth, and Dr. Shoenfeld was asked if this could be a reflection of personal choice. *See* Pet'r's Ex. 129. He clarified that the women had not given birth, and the study did not say if that was by choice. *Id.* He did say that it is "not even plausible" that American women would choose not to give birth in numbers similar to the baby boom period and noted he would need to see proof that it was by choice. Tr. 297:3–7. Dr. Shoenfeld stated that "association is not causation." Tr. 299:7–8. However, he opined that "in light of the fact that papillomavirus can cause infertility, previous papers, and the association, it doesn't show causation, but it's close to causation." Tr. 299:4–7.

Following a discussion of one of his articles that was withdrawn from publication consideration, Dr. Shoenfeld testified that there are few studies to support his theories, because "the editor[s] of journals do not like to publish anything which says something wrong about

[41] Citing Pet'r's Ex. 129, ECF No. 112-1, DeLong, G., *A lowered probability of pregnancy in females in the USA aged 25–29 who received a human papillomavirus vaccine injection,* 81 J. TOXICOL. ENVIRO. HEALTH 661, 661–674 (2018).

vaccine." Tr. 270:25, 271:1–2. He noted specifically, "plenty of articles which the title of them is adjuvant-induced autoimmunity." Tr. 303:8–10.

Lastly on direct examination, Dr. Shoenfeld discussed genetic preponderance to autoimmune disease. He identified the HLA-DRB1 haplotype that is "very, very, very prevalent among all autoimmune diseases." Tr. 273:5–6. Individuals like Petitioner "have even higher prevalence of this HLA-DRB1 genetic marker," and often develop several autoimmune diseases over the course of their lifetimes. Tr. 273:20–21. Dr. Shoenfeld also noted that women of childbearing age "have a more aggressive immune system[, a]nd that's what makes them more prone to develop autoimmune disease." Tr. 274:20–23. The individuals "are at risk when they are exposed to environmental factor which can be the adjuvant, can be infectious agents which constitutively contains adjuvants, et cetera." Tr. 275:3–6.

On cross-examination, Dr. Shoenfeld was asked if his theory could be applied to every vaccine and any autoimmune disease. Tr. 281:20–21. He stated that in someone with a genetic predisposition, the answer is yes. Tr. 283:4–6. He explained that any bacteria or viruses with peptide chains that are susceptible to cross-reactivity and then incorporated in full or in part into vaccines can cause autoimmune disease if an "externally strong adjuvant has been added to them." Tr. 282:16–23.

Dr. Shoenfeld conceded that there has never been a study that has shown the HAV induces the production of MCM8 autoantibodies, however, he noted that knockout mouse models have been done and are good analogies because "there is a great similarity between binding of a destructive autoantibody and killing the enzyme by knockout." Tr. 286:8–10. For this theory to work, Dr. Shoenfeld emphasized that all three mechanisms must work together in someone with a predisposition. He testified "that most probably following the aluminum direct toxicity and destr[uction] of the cells, there was even definitely much more exposure of the enzyme to the immune system." Tr. 288:6–9. This, he continued, is "part of the enhancement of the autoimmune mechanism and the molecular mimicry in this case." Tr. 288:9–11.

Dr. Shoenfeld testified that there is no difference between the manifestation of autoimmune POI and POI caused by other factors. In cases of someone with a predisposition like Petitioner, her history and comorbidity reveal that her POI is autoimmune. Tr. 292:24–25, 293:1. Although molecular mimicry and adjuvant enhancement are both theories that can stand by themselves to explain vaccine-induced autoimmune disease, Dr. Shoenfeld opined that in Petitioner's case, "the two or three plausible mechanisms played in concert to enhance it." Tr. 303:18–20. Because of her history, Dr. Shoenfeld believed that even without POI, Petitioner may have developed Hashimoto's thyroiditis independently as a result of the vaccine. Tr. 305:2–3. However, Dr. Shoenfeld would say "in parallel [instead of independently] . . . [he] would use the word parallel." Tr. 305:4–5.

iii. Dr. Steven Pike (Petitioner)

Dr. Pike wrote that the purpose of his report "is to describe what efforts have been undertaken to determine the safety of adjuvants used in vaccine products . . ." Pet'r's Ex. 92. He noted that randomized trials and epidemiological studies are not available to support his

conclusions, because they don't exist. *See id.* However, he is not suggesting "that vaccines not be used, including the [H]epatitis [A] vaccine that is the vaccine this claimant argues caused [A.D.'s] injury . . ." *Id.* at 3.

In support of his opinions regarding aluminum exposure, Dr. Pike relied on animal studies, writing "aluminum does cause perturbations of the pituitary-gonadal axis and causes morphological changes to ovaries." *Id.* He continued, writing that human studies are not available due to the extreme rarity of "individuals having unusual susceptibility or sensitivity or vulnerability to vaccine components" coupled with "unique timing or cofactors . . . or to a triggering of a pre[-]existing potential for ovarian insufficiency." *Id.* He noted that an occurrence of once in a million would cause an event only one thousand out of one billion times. *Id.* The lack of studies that focus on the relationship between POI and vaccination is not proof that such a relationship does not exist. *Id.*

His report acknowledged that "[m]any cases of ovarian insufficiency have no cause." *Id.* at 4. He focused on the importance of the temporal relationship that "alone is insufficient to determine causation, [but] it is [still] a very substantial factor." *Id.* Dr. Pike went further, noting the association of bee stings with respiratory distress due to a temporal relationship and argued that "[i]n this case temporality is met because the vaccine administration preceded the emergence of POI[;] the rate of development of POI was not a sudden event, but rather, developed over a time period consistent with an immune response mechanism . . ." *Id.*

The report then shifts to aluminum and its effects on the body. *See id.* Dr. Pike gave a general overview of how much aluminum is present in the body at any given time and noted that it is "mostly bound to the skeleton (~50%) and lung (~25%)." *Id.* at 5. He noted that aluminum is present in the body in "relatively large amounts" compared to other minerals due to the human body's immunological tolerance of aluminum protein complexes. It "inhibits several cellular enzymes and neurotransmitters," and "binds to DNA, RNA, and nucleotides and many proteins." *Id.* at 6. Dr. Pike explained that "[a] local increase in aluminum would induce new protein complexes," and it is used as an adjuvant to "induce and enhance an immune response to the aluminum antigen complexes that are injected during vaccination." *Id.* at 6–7.

Dr. Pike then turned to how the aluminum adjuvant in a vaccine is processed in the body. Dr. Pike cited the Keith et al.[42] study that reported "[o]ver 50% of the adjuvant transferred from the antigen to the interstitial or serum protein within 15 min." *Id.* at 5. He continued that "Al3+-antigen complexes separate at the local injection site and free Al3+ is available to bind with other local proteins or proteins that may be circulating in the blood." *Id.* at 7. Consequently, "[t]he specific molecular complex presented to [antigen presenting cells] is one mechanism by which aluminum can produce an adverse effect through [] immunologically mediated and amplified process . . . another mechanism for adverse effect may be through a direct toxic effect of the metal itself interacting with key biological components of a cell." *Id.*

[42] Citing Pet'r's Ex. 95 at 2, ECF No. 73-2, Keith, L.S., et al., *Aluminum toxicokinetics regarding infant diet and vaccinations,* 20 VACCINE 13, 13–17 (2002).

The Anacletus et al.[43] and Chinoy et al.[44] rat studies were also cited in Dr. Pike's report to illustrate aluminum's effect on ovarian cells. *Id.* Rats in the Anacletus study "demonstrat[ed] a direct toxic effect of aluminum on ovarian cells," while the rats studied in the Chinoy study experienced "significant decreases in serum estradiol, ovarian production," and overall impaired ovarian function. *Id.* Both groups received aluminum in doses of 200 mg/kg. *Id.* Dr. Pike noted that these rats received cumulative doses, but he found that difference irrelevant. *Id.* What Dr. Pike focused on "is the blood concentration and tissue sequestration." *Id.* at 8. He stated that there is a "lack of published research that have studied the toxic effects of aluminum to humans from different routes of exposure and to different organs." *Id.* at 10. During his testimony, Dr. Pike conceded that there were no reliable human studies that could identify a "targeted endpoint" of exposure to aluminum that a human body could safely absorb at any specific time. Tr. 141:3–5. Specifically, "[n]o studies were located regarding reproductive effects of various forms of aluminum following acute, intermediate, or chronic duration oral exposure in humans." Tr. 143: 11–14. Despite "[n]eurological, neurobehavioral, and cognitive impairment" associated with aluminum exposure, Dr. Pike wrote that "[a]luminum in products has been presumed safe because it fell into the 'generally accepted as safe' (GRAS) exception when the Food and Drug Act was enacted." Pet'r's Ex. 92 at 17. He testified that aluminum has never been tested for safe use as a vaccine adjuvant. Tr. 137:17–20. Dr. Pike continued that "within 15 minutes, 50 percent of the adjuvant is gone into the interstitial proteins and serum proteins and distributing throughout the body." Tr. 145:5–7. This means that "the biggest contribution to body burden of aluminum in infants was from vaccination." Tr. 146:2–23. Dr. Pike also noted no studies that identified signs of autoimmune disease in children following HAV or POF following HPV. Pet'r's Ex. 92 at 17.

Dr. Pike testified that some studies demonstrate "that aluminum is toxic to gonadal tissue, and the gonadal tissue in the male is not that much different from the female in many respects." Tr. 151:3–6. The Sun article,[45] for example, reported that "as the dose goes up, the magnitude of the effect, the deleterious effect — that is, the inability to produce testosterone but the testes — increases." Tr. 152:4–7. Dr. Pike also described a second effect "not only on the testes but on what we would call the hypothalamic gonadotropin axis." Tr. 152:8–9. The Sun study also provides "morphological evidence of damage to the androgen receptor . . . endocrine damage in the form of inability to functionally produce testosterone, . . . [and] pituitary damage in the inability of the pituitary gland to respond to the lowering testosterone levels." Tr. 154:10–15. Dr. Pike testified that "[i]n [his] report, [he] mention[ed] that what's really important and what we actually don't know in any of these animal studies and what we don't know in the case of [Petitioner] is what the actual concentration of the aluminum was at the target where the action took place." Tr. 160:23–25, 161:1–2.

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[43] Citing Pet'r's Ex. 97 at 1, ECF No. 73-4, Anacletus, F.C., et al., *Evaluation of Aluminum Toxicity and the Ameliorative Effect of Some Selected Antioxidants on Reproductive Hormones and Organs of Female Wister Rats,* 7:3 BR. J. PHARMACOL. TOXICOL. 26, 26–30 (2016).

[44] Citing Pet'r's Ex. 98, ECF No. 73-5, Chinoy, N.J., et al., *Effects of Sodium Fluoride and Aluminum Chloride on Ovary and Uterus of Mice and Their Reversal by Some Antidotes,* 34:1 FLUORIDE 9, 9–20 (2001).

[45] Citing Pet'r's Ex. 77, ECF No. 96-9, Sun, H., et al., *Effects of Aluminum Exposure on Serum Sex Hormones and Androgen Receptor Expression in Male Rats,* 144 BIOL. TRACE ELEM. RES. 1050, 1050–1058 (2011).

Dr. Pike further relied on the Anacletus et al.[46] study because it used female Wister rats to "look[] at the effect that aluminum had on actually the reproductive hormones and the reproductive organs." Tr. 161:19–20. Ultimately, the study revealed "a decrease in the production of progesterone in the aluminum-fed group compared to the control," Tr. 162:10–11, and "a lot of damage to the ovarian cell structure, the stroma[.]" Tr. 162:17–18. Dr. Pike concluded there is "a mechanism for the toxicity of aluminum in some form of oxidative stress." Tr. 163:1–3. He indicated that multiple mechanisms, working in concert, may increase the risk of increased production of autoantibodies, including molecular mimicry. Pet'r's Ex. 92 at 17.

A description of molecular mimicry consistent with the other experts' writings was provided by Dr. Pike, and he noted that the Christen et al.[47] authors concluded "molecular mimicry might, in some cases be more efficient than molecular identity to trigger autoimmunity, because tolerance induction to 'almost-self' antigens can be less efficient . . . to true autoantigens." *Id.* at 20. Dr. Pike addressed the criticism in A.D.'s case that the temporal relationship is too short by opining that "[t]here is no basis for tying the rate of an immune system response to Hepatitis A antigens to the rate of development of either a direct toxic effect or direct autoimmune effect of the vaccine or its components." *Id.* at 22. He continued that an appropriate immune response to vaccination may very well occur months prior to an adverse effect. *Id.* Dr. Pike also wrote that "the development of POI need not be an all-or-none event," and that the increase in antibody titers would also increase "their action and toxic effect on ovarian function [would] gradually rise." *Id.* This gradual increase in pathogenesis is consistent, Dr. Pike argued, with A.D.'s "development of first irregular menses, then eventually amenorrhea a few months later." *Id.*

Dr. Pike drew an analogy between HPV and HAV because they are both viral-based immune system provocations with aluminum adjuvants. Tr. 169:10–14. "They have the same incipients, as they're usually called, and incipients are supposedly inert, but we know that's not true." Tr. 169:19–21. He explained that "if there are other antigens in the milieu around where that adjuvant is, then the immune system is not highly selective in what it's going to respond to." Tr. 170:5–7. He continued that "the antigen processing cells are going to present this antigen to the T and B cell population." Tr. 170:9–10. Dr. Pike was unable to explain why there aren't significantly more POI cases following HAV than HPV, given that HAV has been around much longer. He testified that he "would defer to [his] esteemed experts in both autoimmunity or autoimmunology and reproductive medicine." Tr. 171:3–5.

Dr. Pike also discussed A.D.'s predisposition and wrote that she is more likely "to be sensitive than others to the emergence of autoimmunity and may be expected to have more circulating autoimmune antibodies to various self-antigens." Pet'r's Ex. 92 at 23. He continued that "[a]djuvants present in a vaccine would be more likely to encounter circulating self-antigens, autoimmune antibodies and their B-cell clones, and thus more like[ly] to induce an immune response to circulating self-antigens." *Id.* He wrote that her immune system "produced activated T cells and B cells that could have cross-reacted with 'self-proteins'. . . through . . . molecular mimicry that could have attacked ovarian cells, or could have stimulated an increase in already present and circulating autoreactive antibodies through clonal expansion mechanisms." *Id.* at 27.

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[46] *See* Anacletus, F.C., et al., *supra* note 43.

[47] Citing Pet'r's Ex. 105, ECF No. 74-2, Christen, U., et al., *Viral triggers for autoimmunity: Is the 'glass of molecular mimicry' half full or half empty?,* 34 J. AUTOIMMUN. 38, 38–44 (2010).

The other mechanism that Dr. Pike focused on is oxidation. He explained that "aluminum has the capacity to work in — by entering complexes with specifically citrate, to react with iron and have iron produce these hydroxyl radicals." Tr. 176:4–7. This causes a superoxide formation. Dr. Pike continued that "there's an extra electron on an oxygen atom associated with the aluminum" that is donated to iron already present in the body. Tr. 10–11. This iron engages in a feedback loop whereby it continuously reacts with hydrogen peroxide to form "free radicals of hydroxyl [that] go on to cause damage." Tr. 176:16–17. The "cycle just continues and continues and continues, and it just pumps hydroxyl free radicals over and over . . ." Tr. 176:20–22. Dr. Pike testified that this process is "how one atom of aluminum can continue to produce tremendous oxidative damage to cellular membranes, DNA in the nucleus, because the aluminum is found in the nucleus, in the cytoplasm, in organelles . . . [and] affects metabolism," and interferes with the inner workings of cellular machinery. Tr. 176:24–25, 1771–5.

In summary, Dr. Pike testified that "none of [Petitioner's] excellent doctors have found an explanation." Tr. 173:11–12. He concluded that "in this case, we have the vaccine, we have certain temporality relationships, [and] we have certain mechanisms that are plausible biologically." *See id.*

Dr. Pike was asked about his credentials and prior expert testimony on cross-examination. He admitted that he has never published on aluminum toxicity or vaccine reactions. Tr. 181:5–18. Dr. Pike was also asked if his expert opinion was excluded for being unreliable. When presented with specific cases, Dr. Pike confirmed that he was allowed to testify but was unsure if his testimony was ultimately considered. *See generally* Tr. 185.

In light of his testimony that he is unable to say what amount of aluminum exposure is safe, Dr. Pike was asked the basis for his opinion that the amount Petitioner received was pathogenic. Dr. Pike first noted that aluminum is known to cause toxicity affecting the reproductive organs, interfere with hormone production, and cause tissue damage. Tr. 187:20–25, 188:3–6. Dr. Pike then reiterated that aluminum can undergo the Fenton reaction, whereby hydroxyl radicals are "created in huge amounts." Tr. 188:17. These hydroxyl radicals can do damage to "a membrane [] bi-lipid layer, . . . or let's say a structural protein or an enzyme that's involved in the production of reproductive hormone." Tr. 188:21–25, 189:1. Lastly, Petitioner "is an individual who has . . . [a] hereditary predisposition to autoimmunity based on family history." Tr. 189:8–11. As a result, Dr. Pike reasoned that "she apparently is a highly susceptible individual that reacts at doses that most individuals who receive the vaccine would not react to." Tr. 189:12–15. All in all, Dr. Pike opined the occurrence is rare but biologically plausible. Tr. 190:16–17.

Dr. Pike was then asked how to reconcile Petitioner's elevated FSH and LH levels with the study results that suggest these levels should be decreased due to pathogenesis. He testified that "it's hard to, of course, apply an animal study to a specific human individual and their particular problem medically." Tr. 196:2–4. Every individual is different and "[i]t may very well be that there's a combination of factors here that includes not only the aluminum toxicity as an atom, a molecule, but also the immunological process." Tr. 198:13–16. Dr. Pike stressed that these processes are "so complex that we don't really understand it." Tr. 198:18–19. He agreed that his opinion in this case would apply to any vaccine that contains an aluminum adjuvant and "suggest[ed] . . . that's a reasonable hypothesis that should be tested." Tr. 199:6–8.

The temporal relationship between vaccination and POI onset is not the only thing that Dr. Pike said he relied on. He noted "the strength of the association of aluminum with the toxic endpoints in testicular and ovarian tissues and the effects it has on hormonal levels . . . we didn't go into a whole lot of things that we could have gone into, but there's strength in the association of aluminum and those effects." Tr. 201:14–20. Although he conceded that he is not aware of [a]luminum toxicity being listed as a cause for POI, he noted that as it applies to Petitioner's case, "at some point in time, when you've exhausted the universe of causes and you have one thing left and that one thing is shining like a beacon, you just can't ignore it." Tr. 202:12–15.

Dr. Pike was asked to quantify the temporal relationship in this case. He testified that "the injury occurred the moment the vaccine was given, and it continued until the point in time that she — that she was — in fact, it may even still be continuing." Tr. 204:20–23. He asserted that "[t]he reactions of the immune system are happening instantaneously." Tr. 204:6–7. He noted, however, that "[i]t takes time for [the vaccination to initiate processes that] produce the degree of damage that finally exhausts the organ." Tr. 204:8–11. When pressed for a specific number, Dr. Pike said, "[h]is time frame is within a few weeks of the administration of the vaccine through I think whatever was the [seventy-two] days afterwards." *See id.* He ultimately admitted that he did not know how long it would take for POF symptoms to develop following vaccination. Where aluminum is in proximity to ovary cells or tissues, "[aluminum toxicity] is instantaneous." Tr. 205:18–20.

Following up on Dr. Pike's testimony that there would be an instantaneous effect at the time of vaccination, he was asked if there should be a localized reaction at the injection site. He testified that there "would also have [to be a] location reaction[]," but the aluminum would likely travel to organs with a heavier blood supply. Tr. 208:7. Dr. Pike was asked why we didn't see evidence in this case of a localized reaction or evidence of damage to other organs with a heavier blood supply. He admitted that he "[didn't] really know how to answer." Tr. 210:2–3. Eventually, he noted that "[m]any organs have reparative processes where they can repair themselves," and "you may not necessarily see clinical evidence of damage in some of these organs." Tr. 214:11–13.

Finally, Dr. Pike suggested that molecular mimicry works in conjunction with the aluminum reaction to cause POF. However, he testified that he did not know if both processes were needed to to trigger POF in the present case.

iv. Dr. Patrizio Caturegli (Respondent)

Dr. Caturegli's first written report noted the lack of scientific studies linking HAV with POF or Hashimoto's thyroiditis and the rarity of any adverse event following a HAV. Resp't's Ex. A at 3–4. He then noted that if systemic activation caused autoimmunity, it would occur more frequently and would have occurred following one of the many other vaccinations that A.D. received. *Id.* at 4. Similarly, he opined that molecular mimicry would require a stretch of amino acids that is longer than the one identified by Petitioner's expert. *Id.* Moreover, the shared epitopes "would have to be present in both the ovary and the thyroid." *Id.* Lastly and "most importantly," Dr. Caturegli wrote that the temporal relationship was inappropriate. *Id.* at 4–5. Based on A.D.'s family history and clinical progression, "it takes years before the [autoimmune] disease becomes

clinically overt and gets diagnosed." *Id.* at 5. Specifically, Dr. Caturegli expects to see a time period on the order of three to ten years and at least seven years before any diagnosis of Hashimoto's thyroiditis can manifest. *Id.* This is much longer than A.D.'s timeframe.

In a responsive expert report, Dr. Caturegli reiterated his augments regarding the lack of scientific data to support a causal relationship between HAV and POI via molecular mimicry. Resp't's Ex. E. He briefly mentioned that if adjuvants induced POF, there would also be more scientific data in support and the case numbers would be higher due to the number of vaccines that are administered that contain aluminum adjuvant. *Id.* at 2.

Dr. Caturegli took the stand and was qualified as an expert in immunology and endocrinology. Tr. 396:15–17. Dr. Caturegli testified that Petitioner suffered from Hashimoto's thyroiditis. Tr. 397:13. He noted that Hashimoto's thyroiditis, like other classic autoimmune diseases, often has idiopathic origins. Tr. 397:19–20. He explained that "[f]or the pathogenesis, . . . we know that they arise from a combination of three factors: [t]he patient's genes, the patient's (sic) immune system[,] and the all-encompassing being of the environment." Tr. 398:2–6. Dr. Caturegli explained that out of about one hundred autoimmune diseases, "antibodies are pathogenic only in a few. But antibodies are present so can be used as a diagnostic marker in all of them." Tr. 398:17–20. He testified that the common antibodies that we see in Hashimoto's thyroiditis are thyroperoxidase[48] and thyroglobulin,[49] and they are not pathogenic. Tr. 399:4–7. Dr. Caturegli was not aware of Hashimoto's thyroiditis resulting from Hepatitis A infection or HAV. Tr. 399:20–25.

Dr. Caturegli testified that he was unable to conclude that HAV can cause Hashimoto's thyroiditis, even if he assumed that it caused autoimmune hepatitis, because "the immune system is specific," Tr. 400:25, and "autoimmune diseases . . . have a target organ." Tr. 400:18–19. He continued, "so the fact that in this case the vaccine could cause liver damage doesn't translate to the fact that vaccine could cause thyroid damage or ovarian or testicular damage." Tr. 400:20–23. He conceded that Petitioner's Exhibit 21[50] does suggest that HAV can cause autoimmune hepatitis, but Dr. Caturegli was wary. He noted that "[a] single case report is very useful clinical observation and from astute clinician, they are very meritorious, but they don't prove causality." Tr. 402:10–13.

Similarly, Dr. Caturegli did not think the Karali et al.[51] article was helpful. He testified that evidence of antibodies following vaccination shows that the vaccine is working; however, there must be some evidence that the antibodies are connected to some pathological condition. Tr. 402:21–25, 403:1–5. This reasoning continued through Dr. Caturegli's response to Dr. Shoenfeld's theory of molecular mimicry. Dr. Caturegli testified that a blast search conducted to compare the "2,227 letters from the [H]epatitis A virus against one hundred thirty-two million and changes (sic) of human protein" revealed nothing. Tr. 407:24–25, 408:1. When the search engine looked for a

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[48] *See supra* note 18.
[49] *See supra* note 28.
[50] *See* Pet'r's Ex. 21, ECF No. 25-3, Berry, P.A., et al., *Hepatitis A vaccine associated with autoimmune hepatitis,* 13:15 WORLD J. GASTRO. 2238, 2238–2239 (2007) (explaining that "[t]here is substantial evidence favoring [H]epatitis A virus (HAV) as an etiological factor in autoimmune hepatitis (AIH).").
[51] Karali, Z., et al., *supra* note 36.

match to the six amino acid sequence identified by Dr. Shoenfeld, there were one hundred and forty-seven sequences found; however, the program designated all matches as insignificant. Tr. 408:14–16. Dr. Shoenfeld focused on the MCM8 protein that appeared in this search, but Dr. Caturegli questioned why that particular protein was identified instead of one of the one hundred and forty-six others. He further questioned why Petitioner did not develop reactivity against another type of human protein. Tr. 410:13–15. Dr. Caturegli concluded that a six amino acid peptide chain is too short to do a blast search. Tr. 409:20–22. He testified that there is not enough specificity, but also said, "this doesn't disprove that. It's possible. Just say that in my view is unlikely." Tr. 410:22–23.

According to Dr. Caturegli, Petitioner first had clinical symptoms of her Hashimoto's thyroiditis on February 26, 2014. He explained that in a normal individual, the thyroid gland is soft with collagen fibers. Tr. 411:17–18. An immune process can cause damage, and the thyroid's consistency can harden into a rubber-like consistency. Tr. 411:28–21. Dr. Caturegli opined that "a very hard consistency [] suggests that the [immune] process has been ongoing since several years." Tr. 411:23–24. This is evidence that "[i]t's been a long chronic type of condition." Tr. 411:23–24. Dr. Caturegli also pointed to a "very high level of antibodies against TPO[, which] means a flared, very active type autoimmune process that has been ongoing since a long time." Tr. 412:9–12.

There were two studies that Dr. Caturegli relied on to establish an appropriate timeline for the development of autoimmune disease. The first study, by Rose et al.,[52] wherein Dr. Caturegli participated, analyzed stored blood samples of U.S. soldiers. *See* Resp't's Ex. A at 5. The individuals that developed thyroiditis, "already had the indication of TPO antibody presence elevation at a mean of seven years before the clinical diagnosis." Tr. 415:18–20. The analysis was repeated for individuals who developed lupus. One of the researchers "went back in time and checked [the blood samples for these soldiers] that — showed the same thing: antibodies against different lupus species were present well in advance of the clinical diagnosis." Tr. 1–4. Dr. Caturegli testified that this type of analysis was also done with similar results for type 1 diabetics. Tr. 416:6. As a result, it is possible to "have a phase where the function of the gland is normal, but you have ongoing autoimmunity." Tr. 418:16–17. Dr. Caturegli stated that this phenomenon also occurs with Hashimoto's and could apply to Petitioner. Tr. 418:7–25. In his later testimony, Dr. Caturegli further explained that "there is a spectrum of different patient phenotypes where older patients have the classical fibrotic form[, w]hereas the younger patient, [like Petitioner] they have the more pure lymphocytic form." Tr. 446:24–25, 447:1–3. Other signs that Petitioner was experiencing autoimmunity, according to Dr. Caturegli, included a report of urticaria,[53] dermatitis, and psoriasis. Tr. 419:1–7.

Under cross-examination, Dr. Caturegli admitted that he has never treated or even seen a patient with POI. Tr. 424:11. When asked to confirm the assertion in his expert report that Petitioner's POI was autoimmune, he pointed out his lack of experience. He stated, "I agree that thyroiditis is autoimmune in nature. At the time I wrote, the same thing for POI[, b]ut I am not an

[52] Citing Resp't's Ex. A3, ECF No. 104-3, Rose, N., et al., *Significant of Prediagnostic Thyroid Antibodies in Women with Autoimmune Thyroid Disease,* 96:9 J. CLIN. ENDOCRINOL. METAB. 1466, 1466–1467 (2011).

[53] Urticaria is "a vascular reaction in the upper dermis, usually transient, consisting of localized edema caused by dilatation and increased capillary permeability . . ." *Dorland's* at 2011.

expert[; p]robably a mistake." Tr. 20–22. Dr. Caturegli also agreed that Petitioner had a predisposition and stated, "that's one of the most evident things from our clinical experience, familial disposition." Tr. 425:16–17.

Dr. Caturegli reiterated that most autoimmune diseases are idiopathic, and consequently, "[i]n general for thyroiditis, we don't know what's the beginning, what starts." Tr. 426:6–7. He noted that the development of these types of diseases is multifactorial, Tr. 426:12–13, and have long latency timeframes. Tr. 427:11–20. When asked how Guillain-Barré syndrome[54] ("GBS") can develop quickly, Dr. Caturegli clarified what he considered to be an autoimmune disease. He asserted that "autoimmune disease means that there has to be pathological damage in the target organ[,] and you have to see presence of lymphocytic infiltration in those, whatever organ is targeted." Tr. 428:21–24. He opined that "if you don't have that, then it's more difficult to claim autoimmune nature of the condition." Tr. 429:11–13. When asked about Sydenham chorea,[55] Dr. Caturegli asserted that "to characterize something as autoimmune disease in pathology, you want[] to see the disease in the tissue." Tr. 430:10–11. He explained further, "if you define just the presence of antibodies, then I could say yes, you are right, three weeks is exactly what Dr. Shoenfeld described. But if you want to define the disease as infiltration of the target organ with the patient's own immune cells, then I would say no." Tr. 430:13–18. Without confirmation of this infiltration in the ovaries, any designation of POI as autoimmune is based on "circumstantial evidence, and then the argument becomes more tenuous and everybody can have different views about it." Tr. 431:6–8.

When asked if infections and vaccines with the same antigenic material can lead to a similar response in the body, Dr. Caturegli indicated that a "real virus is a live being." Tr. 433:10. In contrast, "when you vaccinate, you inactivate or kill the virus, so you have a different representation of that organism." Tr. 433:11–13. Dr. Caturegli testified that molecular mimicry is "very attractive intellectually," Tr. 435:7, but he disagrees that it occurs because of sufficient homology between the foreign antigen and the host tissue that causes pathological cross-reactivity. Tr. 435:16–20. He defined molecular mimicry as an "immune system respon[se] against a viral or against an infectious target epitope. Not necessarily identical at the primary sequence level." Tr. 435:22–24. Dr. Caturegli went on to opine that "most of the molecular mimicry articles are . . . thought essay, are conceptual essay, . . . [but] much fewer have actually done the experiment." Tr. 437:3–7. He noted that Dr. Rose has never done homology sequencing experiments to test molecular mimicry on type 1 diabetes patients, although he has written his hypothesis. Tr. 439:5–12. Therefore, Dr. Caturegli characterized Dr. Rose's findings as "an opinion." Tr. 439:12.

[54] Guillain-Barré syndrome is a "rapidly progressive ascending motor neuron paralysis of unknown etiology, frequently seen after an enteric or respiratory infection. An autoimmune mechanism following viral infection has been postulated. It begins with paresthesias of the feet, followed by flaccid paralysis of the entire lower limbs . . . upper limbs, and face[.]" *Dorland's* at 1832.

[55] Sydenham chorea is "an acute, generally self-limited, neurologic disorder seen most often in children between the ages of 5 and 15 years or in women during pregnancy; it is closely linked with rheumatic fever. It is characterized by involuntary movements that gradually become severe and affect all motor activities, including gait, arm movements, and speech. A mild psychic component is usually present. It may be limited to one side of the body…or may take the form of muscular rigidity . . ." *Dorland's* at 354.

Dr. Caturegli reiterated that he did not believe that sufficient studies have been done to show that a six-sequence homology is sufficient for molecular mimicry. He noted that MCM8 is present in higher concentrations in organs other than the ovary and questioned if "the immune system [would] first target where the antigen is expressed the most." Tr. 441:3–5.

v. David Frankfurter (Respondent)

Dr. Frankfurter's expert report made the same major points that Dr. Caturegli made, but he focused his arguments more specifically on A.D.'s clinical progression. Resp't's Ex. C. He also noted A.D.'s genetic predisposition, comorbid Hashimoto's thyroiditis, and pre-existing symptoms of slowed growth and proteinuria as evidence that her POI is not vaccine-caused. *Id.* at 5–6.

Dr. Frankfurter's testimony began with a discussion of POI. He defined POI "as amenorrhea before age 40 or four months of amenorrhea before age 40 with at least two independent assessments of FSH as being in the menopausal level." Tr. 18–21. This disease is extremely rare and "[i]n a majority of patients, it is not possible to pinpoint to (sic) precise cause of POI." Tr. 314:23–24. In this case, Dr. Frankfurter noted that Petitioner had begun menstrual cycles; and therefore, her POI is characterized as the secondary type. Tr. 315:13–21. He noted that "there's POI that's associated with autoimmune illnesses and then there is POI that is definitively related to an autoimmune process within the ovary or an inflammatory process within the ovary that's commonly referred to as oophoritis." [56] Tr. 316:1–5. The determining factor, according to Dr. Frankfurter, "if we are going to call something autoimmune POI . . . is evidence of adrenal involvement." Tr. 316:10–12. He relied on a table within a paper by Dr. Lawrence Nelson,[57] that provided "a mechanistic and causative depiction of POI." Tr. 317:4–5. Dr. Frankfurter testified that autoimmunity is evidenced by "a lymphocytic or infiltrative process within the ovary causing inflammation." Tr. 317:6–8. He noted that "[t]he presence of anti[-]adrenal antibodies strongly implies autoimmune oophoritis as the cause of POF," Tr. 318:20–22, but "[t]he presence of thyroid autoantibodies does not prove autoimmune ovarian failure." Tr. 319:2–3. Thyroid autoantibodies can "identif[y] women at risk for developing autoimmune thyroid disorders." Tr. 319:3–4. There is not, however, the "100 percent correlation" between anti-adrenal antibodies and oophoritis. Tr. 321:15. Dr. Frankfurter testified that it can be challenging to distinguish autoimmune POI from a non-autoimmune version, "because the time course between when you see amenorrhea and when you develop anti-adrenal antibodies can be so long that you have a period where it's gray and you don't know." Tr. 322:6–9.

He noted that autoimmune POI "may be triggered by a virus or a failure in the regulation of the immune system." Tr. 319:19–20. The fact that someone already has an autoimmune disease, is not enough, however, to conclude that comorbid POI is autoimmune in nature. Tr. 322:18.

In rebuttal to Dr. Shoenfeld, Dr. Frankfurter discussed the significance of the MCM8 protein. MCM8, he explained, is a protein "used to repair DNA . . . during egg development." Tr. 323:3. Because egg development is complete at the time of birth, the process by which MCM8 is

[56] Oophoritis is "inflammation of an ovary." *Dorland's* at 1323.
[57] Citing Resp't's Ex. C2, ECF No. 104-5, Nelson, L., *Primary Ovarian Insufficiency,* 360:6 N. ENGL. J. MED. 606, 606–608 (2009).

needed to repair any damage done by DNA recombination in order for eggs to mature is also complete. Tr. 324:4–12. Consequently, "you see very little MCM8 expression in the human ovary." Tr. 324:13–14. Conversely, men continue to generate sperm throughout life. Tr. 325:5. During development, sperm "are undergoing myosis, and MCM8 would be expressed" in high levels in the testicle. Tr. 325:6–10. Dr. Frankfurter argued that if components of HAV cause damage to MCM8 and ultimately result in POI, there should also be evidence of analogous damage in testes. Tr. 325:7–18. Such evidence was not presented, and Dr. Frankfurter does not believe it to exist. Tr. 325:13–14.

The evidence presented by Dr. Shoenfeld to support his argument that there is cross-reactivity between the MCM8 protein and a component of HAV is misapplied in Dr. Frankfurter's opinion. Dr. Frankfurter noted that the case studies presented by Dr. Shoenfeld involve three sisters with sexual infantilism. Tr. 326:3–5. In those cases, "the insult is at the point of egg development, so you don't get the appropriate complement of eggs." Tr. 326:7–9. These cases involve primary amenorrhea where the eggs can't develop properly without MCM8. Dr. Frankfurter explained that Petitioner suffered from secondary amenorrhea, and "it would be very unusual for [Petitioner] to have an issue with her MCM8 enzyme." Tr. 326:9–13.

Dr. Frankfurter testified that there was no persuasive evidence presented that established HPV as an appropriate comparative vaccine to HAV. He asserted that the only similarity between the two is that they are both vaccines and said that "as far as the etiologic agent, these are two distinct entities." Tr. 327:9–12. When asked about the evidence filed by Petitioner to suggest that increased infertility is directly related to an increase in these vaccinations, Dr. Frankfurter characterized Dr. Gail DeLong's writing as a "disaster." Tr. 327:19. It does not control for "the greatest increase in the use of long-acting reversible contraceptives or LARCs, as well as . . . the increased desire to avoid pregnancy because of the economic collapse." Tr. 16–19. He also noted that Dr. DeLong's study did not mention POI or make any findings about infertility. Tr. 329:2–6.

Petitioner's clinical presentation was also discussed by Dr. Frankfurter. Petitioner's bleeding, he explained, is likely due to "the medication regimen that she was on." Tr. 332:18. He explained by way of background that "estrogen gets to the uterus and causes the endometrial lining, the functioning tissue that allows implantation of an embryo to proliferate." Tr. 330:19–21. He continued that this proliferation is usually balanced with progesterone to regulate the maturing of this lining and prevent the abnormal growth that can lead to disease. At the appropriate time during a women's menstrual cycle, progesterone will withdraw and the lining that has developed for implantation will shed. Tr. 331:18–21. If this process is missing the necessary components at certain stages of the cycle, persistent proliferation can occur and "a piece of the lining can outgrow its blood supply." Tr. 332:2–4. This can lead to "tissue destruction beyond where the overgrowth is in shearing, then you get profound bleeding." Tr. 332:4–6. Dr. Frankfurter stated that "there was an exchange of time where [Petitioner] was being replaced with transdermal progesterone. The dose, the amount, the duration of time of exposure to the uterus . . . hasn't been established," and could have caused Petitioner's heavy bleeding. Tr. 322:10–12.

During his testimony, Dr. Frankfurter noted that because Petitioner "has not had a positive screen for anti[-]adrenal antibodies, it is very difficult for me to classify what she has as autoimmune [POI]." Tr. 332:21–24. He conceded that Petitioner "clearly has autoimmune

involvement," Tr. 336:14, but he stopped short of "calling this an autoimmune oophoritis that led to her depletion of eggs[.]" Tr. 336:20. Dr. Frankfurter opined that Petitioner "has associated autoimmune illnesses, but it is very difficult to pinpoint at this point in time six years after the initial diagnosis with no evidence of anti[-]adrenal antibodies that she has autoimmune oophoritis." Tr. 337:7–10. He acknowledged that Petitioner's condition could ultimately be autoimmune because the antibodies can appear after the POI diagnosis.[58] Tr. 339:8–14.

Dr. Frankfurter was asked about the temporal relationship between Petitioner's HAV and the onset of her symptoms. He noted that her first symptom was her irregular menstrual cycles in August of 2013 and noted that is "too rapid [of an] onset" to be vaccine caused. Tr. 341:8. Dr. Frankfurter explained, "[a]s far as latency, one would expect then that if you have a syndrome that's clearly associated with autoimmune oophoritis and that can take years to decades, how do you explain two weeks?" Tr. 341:21–24. He believed that two to six weeks is not enough time "to deplete her total follicular cohort." Tr. 342:16–17. Dr. Frankfurter also pointed to "an alteration of [Petitioner's] growth curve about a year before [vaccination]" as a relevant symptom of oncoming menopause. Tr. 343:23–24. He explained that "estrogen closes the growth plate." Tr. 344:7. He concluded that "if well before she manifests the overt sign of amenorrhea, [Petitioner] has a great fluctuation in her estrogen levels, it can affect her growth, which would put that at about a year before her vaccine." Tr. 344:9–13.

Lastly, on direct examination, Dr. Frankfurter explained that "in childhood, you see an FSH level that's generally in excess of its LH level. Once puberty takes over, it flips." Tr. 346:4–6. Petitioner "flipped back there to a childhood pattern, which is suggestive of a form of hypothalamic ovarian disturbance." Tr. 346:7–10. Dr. Frankfurter testified that "there are certain times in life where this can manifest and certain pathological conditions where it is present." Tr. 346:12–14. He "has seen," he stated "women with frank primary ovarian insufficiency with high gonadotropins[59] who then take on a new job or have problem in their lives where they will automatically start suppressing their gonadotropins . . . her [] levels in August are reflective of that process." Tr. 346:25, 347:1–6. Dr. Frankfurter also pointed to an ultrasound done on February 21, 2014 and revealed that "an ovary [] reduced its normal volume significantly." Tr. 347:14–15. He asserted that "for this to happen in a timeframe that is noted, I think, is pretty accelerated." Tr. 347:15–17.

On cross-examination, Dr. Frankfurter was asked to clarify his position on the etiology of Petitioner's POI. He said, "I would say that this individual has an autoimmune process going on, but I don't necessarily say this is autoimmune POI. It's POI in the presence of an autoimmune illness." Tr. 350:3–6. Dr. Frankfurter opined that "there may be some genetic predisposition," Tr. 353:24–25, to autoimmune illness for Petitioner, but noted that "it generally would require a trigger or an exposure." Tr. 354:4–5. As evidence that this trigger occurred prior to vaccination, Dr. Frankfurter pointed to Petitioner's growth record. He noted that if Petitioner "was showing marked fluctuations in estrogen with elevations in estrogen which is seen in the perimenopausal window, you could hypothesize that she is closing her growth place, and that's why she's deviating from

[58] Citing Resp't's Ex. C at 3, ECF No. 30-3 (indicating that "[b]ased on multiple evaluations and laboratory tests, it is clear that A.D. has POI. The etiology is most likely of an autoimmune nature.").
[59] Gonadotropins are "any hormones that stimulates the gonads, especially follicle-stimulating hormone and luteinizing hormone." *Dorland's* at 797.

her curve." Tr. 357:4–8. Dr. Frankfurter clarified that he "was not saying that she is going to have abnormal height. What I'm saying is there is a trend that begins before the vaccine that can be correlated to a hormonal issue that is related to the ovaries." Tr. 358:10–15. The growth deviation, in Dr. Frankfurter's opinion, answers the question "when is the earliest manifestation of this possible." Tr. 358:22–23. He clarified, "[s]he's normal height[, but w]hat I'm saying is that you have a relationship between a condition and an observation." Tr. 361:18–20.

Dr. Frankfurter agreed when asked if two weeks was enough time for a sufficient antibody presence to engage in an autoimmune process. Tr. 363:23–24. He further agreed that HAV has been documented as a potential trigger for autoimmunity. Tr. 362:13–19. This opinion was tempered with his clarification that he "is not aware, based on [his] assessment of the literature . . . that you have seen an increase in autoimmune disease." Tr. 365:10–13. This process continues to exist "in the realm of very, very rare occurrences . . . [and w]e don't have one in relation to either ovarian failure or testicular failure." Tr. 365:21–24. Dr. Frankfurter asserted that "we are talking hundreds of millions of cases of hepatitis throughout the history of the virus, and we haven't a documented case of gonadal issues related to it." Tr. 373:7–11. He continued that it is also important to remember that "the focus here isn't hepatitis. The focus here is oophoritis." Tr. 373:12–13. Dr. Frankfurter testified that he didn't "know of a report in the literature describing POI or POF where hepatitis is related to the process." Tr. 373:21–23. He questioned why there is no increase in POI cases given that Hepatitis B is a universally administered vaccine. Tr. 374:1–5. Dr. Frankfurter contrasted the hepatitis vaccines with the measles, mumps, rubella vaccine, noting the "association between ovarian insufficiency and mumps." He noted that "if anything was going to mimic an epitope that would be associated with oophoritis, it should be the pathogen that's been demonstrated to cause oophoritis for quite some time." Tr. 375:13–18.

Dr. Frankfurter was asked several questions on cross-examination that were, according to him, best left for an immunologist. Tr. 385:2–3. He was recalled and discussed the significance of the recorded size of Petitioner's ovaries from the February 2014 sonogram. Dr. Frankfurter testified that "in [his] experience as a clinically practicing reproductive endocrinologist, when there are small ovaries, unless they're streaks, you almost never see the radiologist write 'small ovaries.'" Tr. 572:12–15. He explained that the volume is given and that can be compared to the norm. Tr. 572:17–19. He noted that "it is a contradiction in terms to call an ovary dead if it's normal in size[, because i]t can't be dead and normal in size at the same time." Tr. 573:7–9. The size of a dead or "post-menopausal ovary is small," Tr. 573:9–10, because "[i]t doesn't have follicles[.]" Tr. 573:10.

The size of Petitioner's ovaries, according to Dr. Frankfurter, "would be suggestive of low estrogen and burnout of her ovaries, which would put the hypergonadotropism[60] more proximal to the insult but would speak to a significant loss of follicles by that point." Tr. 577:16–19.

[60] Hypergonadotropism is sometimes called "hypergonadism" and is defined as "a condition caused by excessive secretion of gonadal (sex) hormones; manifestations include accelerated . . . sexual development . . ." *Dorland's* at 889.

vi. Dr. Edward Cetaruk (Respondent)

Dr. Cetaruk's reports and testimony served to "review[] the theories presented in [Petitioner's experts'] report[s] and the cited articles in support of [Petitioner's causation] theories to determine if [they] present[] data and/or evidence to provide a scientifically reliable basis for [Petitioner's] claim that the [H]epatitis A vaccine she received on July 13, 2013[,] caused her POI." Resp't's Ex. I at 2. In his first written report, Dr. Cetaruk identified three theories of causation that Dr. Shoenfeld had asserted and discussed two: aluminum adjuvant induced autoimmunity and direct aluminum toxicity. *See* Resp't's Ex. F. Dr. Cetaruk first noted that "ASIA is not a generally accepted medical condition or disease in the United States, and Dr. Shoenfeld has never reliably established that ASIA is indeed a discrete medical condition, or that a causal relationship exists between vaccine adjuvants and the development of autoimmune disease." *Id.* at 4. Citing the National Cancer Institute definition, Dr. Shoenfeld wrote in one of his published papers that an adjuvant as "an agent that may stimulate the immune system and increase the response to a vaccine, without having any specific antigenic effect itself." *Id.* This definition, Dr. Cetaruk explained, is at odds with Dr. Shoenfeld's premise in his current expert reports that "[a]djuvants present in vaccines, including [HAV], are designed to hyperactive (sic) the immune system." *Id.* Dr. Cetaruk asserted that "[i]t is misleading to characterize adjuvant function in one way in an article for the scientific community, and another for his expert report." *Id.* Dr. Cetaruk challenged Dr. Shoenfeld's use of "hyper" when referencing the role of adjuvants, because it can "impl[y] that the immune system is thrown out of balance or is overtly activated by adjuvant to cause injury." *Id.* He clarified that the "addition of an adjuvant to a vaccine is well recognized as a means to elicit an *adequate* response to an antigen where otherwise the immune response would be inadequate." *Id.* (emphasis in original).

Dr. Shoenfeld's theory that aluminum is toxic to the ovaries is presented, according to Dr. Cetaruk, with articles that "do not demonstrate any consistent or significant changes in [LH, FSH, and HGH] hormone levels, especially those involved in ovary function (LH, FSH), due to aluminum exposure." *Id.* at 6. Instead, these articles discuss occupational exposure to aluminum manufacturing workers and welders. *Id.* A study conducted to measure metal exposure in rural Brazilian children also assessed "hepatic and renal function, cognitive ability, and [delta]-aminolevulinate dehydratase (ALA-D) activity." *Id.* at 7. Increased levels of aluminum were found in the drinking water and hair of children, but "the authors showed absolutely no correlation between water and/or hair aluminum levels and/or any pathological condition(s) in the study subjects." *Id.* at 8.

Dr. Cetaruk identified one paper that "clearly attempted to study the potential neurotoxicity of aluminum," but he noted "there is no mention of the reproductive system, aluminum-induced ovarian toxicity and/or failure. *Id.* at 9. The animal studies cited by Dr. Shoenfeld do focus on "aluminum-induced reproductive dysfunction" and found that aluminum can significantly decrease plasma testosterone, FSH, LH, sperm count and other reproductive processes. However, this study, and others that are similar, involve an exponentially larger exposure to aluminum than what is present in the vaccine Petitioner received before there were any effects seen on hormone levels. *See id.* Furthermore, Dr. Cetaruk noted that all of these studies were done on male rats and

do not inform on any potential affect of aluminum on ovaries. The Fu[61] and Wang[62] papers, according to Dr. Shoenfeld, "demonstrated inhibition of reproductive functions in female rats during sub-chronic aluminum exposure in drinking water." *Id.* at 13 (citing to Pet'r's Exs. 82, 83). Dr. Cetaruk took issue with the use of these studies, because unlike a single vaccine injection, these rats were orally exposed to aluminum over a period time. *See id.*

Other studies that examined the effect of aluminum on ovaries specifically, were not scientifically reliable to determine causation in human disease, according to Dr. Cetaruk, because they involved female Nile tilapia fish[63] and isolated Chinese hamster ovary ("CHO") cells.[64] *Id.* at 14. The study that sought to "analyze the cytotoxicity and genotoxicity of titanium oxide (TiO2) and aluminum oxide (Al2O3) nanoparticles" on CHO cells was especially troubling to Dr. Cetaruk because the cells used "are not naturally occurring cells and are an artificially derived hydridoma cell line used as an experimental cellular framework for many types of studies." *Id.* at 15.

During his testimony, Dr. Cetaruk explained how toxicological profiles are developed and measured. He testified that "if the exposure that they've identified [is] able to produce an observed adverse effect in a given model . . . a mouse . . . a rat or some other animal, they'll take that finding, and they'll take the lowest level, and divide it by ten." Tr. 466:20–24. He explained further that the level is then divided by ten a second time "to account for susceptible persons within the general population. He concluded that a minimal risk level ("MRL") is set "many factors lower than the research that they're depending on to get to that level." Tr. 467:3–5. MRLs are determined based on exposure amount and characterized as acute, intermediate, or chronic. Tr. 465:16–20. Dr. Cetaruk explained that there is no MRL for acute exposure to aluminum, and vaccination is simply not comparable to occupational exposure, which can be intermediate or chronic. Tr. 467:17–24.

There are three major sources of aluminum exposure, according to Dr. Cetaruk. He testified that "[p]rimarily aluminum is going to be — our primary exposure is going to be dietary[,] [s]o . . . food or water. Tr. 468:8–10. Aluminum is found in "most foodstuffs" given its ubiquitous nature on Earth. Tr. 468:10–12. Dr. Cetaruk noted that "it's going to be in nearly everybody's water supply." Tr. 468:12–13. He described occupational exposure "if you work in an industry . . . that [] manufactures aluminum, like foundry workers, aluminum welders," and noted that "they have a higher incidence of exposure in the workplace." Tr. 468:18–21. This type of exposure is often through inhalation because, "if you're welding aluminum, you're creating aluminum fumes that you can inhale and absorb through your lungs." Tr. 468:22–24. Lastly, Dr. Cetaruk discussed medicinal exposure, but not here that "there's also other products [in addition to aluminum adjuvants in vaccines] that you might ingest, like antacids have aluminum [or] antiperspirants." Tr. 469:2–3.

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[61] Fu, Y., et. al., *supra* note 38.
[62] Wang, N., et al., *supra* note 39.
[63] Citing Pet'r's Ex. 84, ECF No. 98-6, Correia, T.G., et al., *Aluminum as an endocrine disruptor in female Nile tilapia (Oreochromis niloticus),* 151 COMP. BIOCHEM. PHYSIOL. C. TOXICOL. PHARMACOL. 461, 461–66 (2010).
[64] Citing Pet'r's Ex. 85, ECF No. 98-7, DiVirgilio, A.L., et al., *Comparative study of the cytotoxic and genotoxic effects of titanium oxide and aluminum oxide nanoparticles in Chinese hamster ovary (CHO-K1) cells,* 177 J. HAZARD MATER. 711, 711–18 (2010).

Over the course of a lifetime, Dr. Cetaruk explained that an individual "is going to have specific spots where you'll get a vaccine and for that day, you'll have more [exposure]." Tr. 469:17–19. Most human exposure, however, "is going to be dietary, day in and day out." Tr. 469:22–23. Dr. Cetaruk confirmed during his testimony that "animal studies are helpful in the sense that a lot of the research what we want to do to look at toxicity would not be ethical to do in people." Tr. 470:5–7. He noted that "animal study [should] be designed to mimic gathering human exposure as closely as possible." Tr. 470:14–16. It is also important to control for "[t]he dosing of the compound, both in absolute dose as well as the way the dose is administered over time, [and] the route of administration." Tr. 470:23–25.

As he did in his written reports, Dr. Cetaruk attacked Petitioner's reliance on some of the filed animal studies because the aluminum exposure occurred over time. He testified that "the studies that we looked at were really — they were designed to look at essentially chronic exposure or daily exposure from the diet." Tr. 4–5. Dr. Cetaruk discussed the Sun et al.[65] study and acknowledged that after exposure to aluminum over one hundred and twenty days in three groups: low, middle, and high doses, there was a statistically significant difference in the middle dose group's hormone levels. He added, however, that in that study, "you're looking at not only the absolute dose for, let's say, you know, a daily time frame, but also the cumulative dose over the one hundred and twenty days before you actually do your test, before you test your end points and see if there's a difference." Tr. 477:23–25, 478:1–2. He cautioned, "generally speaking, you can't pick one day out of one hundred and twenty and say, you know this is comparable." Tr. 478:3–4. He continued, "typically if you want to study something that has a single, one-day dose, like in this case . . . you know, what the effects are of a single injection of a vaccine containing aluminum adjuvants, then you'd ideally want to have an animal study that looks at a dose that is one day in duration." Tr. 478:16–21.

The Anacletus et al.[66] study was another study that Petitioner relied on with subjects exposed to aluminum for an extended period of time. Female rats in that study were given 200 milligrams per kilogram of aluminum orally, for six weeks, and Dr. Cetaruk noted inconsistencies in the results but acknowledged the authors detected "changes in the cells of the ovaries at the end of the one hundred and twenty days" called vacuolization. Tr. 480:17–19. Ultimately, they concluded that "aluminum had a deleterious effect on the ovary, which possibly is a result of the aluminum-induced oxidative damage." Tr. 482:4–6. Dr. Cetaruk testified that the "paper doesn't prove that the mechanism of injury is oxidative stress." Tr. 483:19–20.

He stressed the importance of a statistical significance in hormone levels. In the Alessio et al.[67] study they looked at "the effects of aluminum on what we call aluminum manufacturers, as well as they identified a specific group of aluminum welders." Tr. 484:6–8. Ultimately, the authors found "a decrease in TSH, which is thyroid stimulating hormone, which secreted by the pituitary, but it wasn't statistically significant." Tr. 485:1–2. There was no difference found with respect to any of the other hormone levels.

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[65] Sun, H., et al., *supra* note 45.
[66] Anacletus, F.C., et al., *supra* note 43.
[67] Citing Pet'r's Ex. 73, ECF No. 96-5, Alessio, L., et al., *Behaviour of biological indicators of internal dose and some neuro-endocrine tests in aluminum workers,* 80:4 MED. LAV. 290, 290–300 (1989).

Dr. Cetaruk then addressed the Keith et al.[68] article and explained that "the stated purpose of the paper was to really look at the sources of aluminum exposure in the first year of life." Tr. 487:7–9. While the study "looked at the contribution of dietary exposure to aluminum," there was also consideration afforded to "exposure from the vaccinations that would normally be administered" during that time. Tr. 487:11–15. Dr. Cetaruk explained that vaccinations do cause a spike in aluminum levels, but there is no MRL to account for acute exposure, only intermediate and chronic. Furthermore, when the aluminum MRL is reached, that exposure amount is not expected to cause harm. Tr. 487:25. The aluminum that is released into the body after exposure is "going to stay associated with a protein or some other macro-molecule." Tr. 493:21–22. Dr. Cetaruk continued, that "based on the priest studies, 90 percent of the aluminum is gone from the body within days that it's injected. What stays behind becomes associated with certain tissues, primarily the bone, the muscle, and the skin." Tr. 494:19–23. For example, in patients receiving dialysis, aluminum accumulation can lead to a condition called dialysis-associated dementia, because aluminum is considered a neurotoxin. Tr. 496:18–19. Cognitive problems would develop because of aluminum toxicity in the brain. However, when looking at the bone and liver, researchers found aluminum but "no associated inflammation, [and] there was no associated, . . . liver problems, but that's where they were finding this aluminum." Tr. 497:10–13. Dr. Cetaruk reiterated that although aluminum could be present in the body, "there was no pathology associated with its presence," even when injected into the body of primates in the form of an adjuvant. Tr. 498:9–10. He concluded by testifying that animal studies or chronic exposure aluminum studies "definitely have information that is relevant, but not applicable" to establish causation in Petitioner's case. Tr. 502:6–8.

On cross-examination, Dr. Cetaruk conceded that he had not done any research on aluminum, aluminum adjuvants in vaccines, or the nature of a host's immune response to vaccination. Tr. 503:13–25, 504:1–2. He also confirmed that there had not been any safety studies for acute exposure to aluminum that have been filed in this case, despite his assertion that "there's research on acute exposure to aluminum." Tr. 508:17–18. When asked about the studies presented that show a reduction in testosterone levels and LH with an impact on the antigen receptor due to exposure to medium and high levels of aluminum, Dr. Cetaruk noted that in toxicology, "the dose makes the poison." Tr. 517:1–2. He continued that "it's important to point out that the doses being used [to produce these results] are much higher than are seen in the human context." Tr. 517:11–13.

Dr. Cetaruk was also asked about how the metabolism or excretion of aluminum should be accounted for when measuring a cumulative dose. He explained that "elimination of the compound is assumed in every model, Tr. 519:9–10, and noted that "the dose is what goes into the patient, or the animal for that matter, and it's intrinsic to giving the dose is that some of it's going to be eliminated." Tr. 520:1–4. Dr. Cetaruk refused to identify aluminum as an endocrine-disrupting compound in humans but did agree that "it's been theorized as being possible, according to the conclusions of the papers[; s]o it deserves further studies." Tr. 526:9–10.

[68] Keith, L.S., et al., *supra* note 42.

V. Applicable Legal Standard

To receive compensation under the Vaccine Act, a petitioner must demonstrate either that: (1) her condition is a "Table Injury," and therefore resulted from the receipt of a covered vaccine or vaccines within the time frame prescribed by the Vaccine Injury Table set forth at § 14, as amended by 42 C.F.R. § 100.3; or (2) petitioner's condition is an "off-Table Injury," one not listed on the Table, that resulted from her receipt of a covered vaccine. *See* § 11(c)(1)(C); *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1319–20 (Fed. Cir. 2006). Petitioner's claim that her HAV caused her symptoms does not fall within the Vaccine Table. Thus, she must prove that her vaccine was the cause-in-fact of her condition.

To establish causation-in-fact, a petitioner must demonstrate by a preponderance of the evidence that her vaccine was the cause of her injury. § 13(a)(1)(A). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but-for" cause of the injury is enough for recovery. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999).[69] Once a petitioner has proven causation by preponderant evidence, "the burden then shifts to the respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine." *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs.,* 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing §13(a)(1)(B)).

In *Althen v. Sec'y of Health & Human Servs.*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278 (Fed. Cir. 2005). The *Althen* test requires a petitioner to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *See id.* (internal citations omitted).

Specifically, under the first prong of *Althen*, a petitioner must offer a scientific or medical theory that answers in the affirmative the question "can [the] vaccine(s) at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006), *cert. denied*, 551 U.S. 1102 (2007). Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of her claim. *Lampe v. Sec'y of Health & Human Servs.,* 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharms., Inc.*, requires that courts determine the reliability of an expert opinion before it may be considered as evidence. *See* 509 U.S. 579 (1993). "In short, the requirement that an expert's testimony pertain to 'scientific knowledge" establishes a standard of of evidentiary reliability." *Id.* at 590 (citation omitted).

[69] The Vaccine Act also requires petitioners to show by preponderant evidence that the "residual effects or complications" of the alleged vaccine-related injury lasted for more than six months. § 11(c)(1)(D)(i). It is undisputed that this six-month requirement is satisfied in this case.

Consequently, for Vaccine Act claims, a "special master is entitled to require some indication of reliability to support the assertion of the expert witness." *Moberly,* 592 F.3d at 1324. The *Daubert* factors are used in the weighing of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.,* 94 Fed. Cl. 53, 66–67 (2010) ("[U]niquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted."). When both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). And nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

Causation is determined on a case-by-case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioner is not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

In addition to showing that the vaccine at issue can cause a particular injury, a petitioner must also, under *Althen's* second prong, prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1278. A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; the petitioner "must explain *how* and *why* the injury occurred." *Pafford*, 2004 WL 1717359, at *4 (emphasis in original) (internal citations omitted). A reputable medical or scientific explanation must support this logical sequence of cause and effect." *Hodges v. Sec'y of Health & Human Servs.,* 9 F.3d 958, 961 (Fed Cir. 1993) (citation omitted).

To satisfy the third *Althen* prong, a petitioner must establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id.* However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id.*; *see also Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

Although a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory.

See Althen, 418 F.3d at 1278. The special master cannot infer causation from temporal proximity alone. *See Thibaudeau v. Sec'y of Health & Human Servs.*, 24 Cl. Ct. 400, 403–04 (1991); *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("[T]he inoculation is not the cause of every event that occurs within the ten[-]day period . . . [w]ithout more, this proximate temporal relationship will not support a finding of causation." (quoting *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983))).

A petitioner who satisfies all three prongs of the *Althen* test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Human Servs*., 98 Fed. Cl. 719, 726 (2011). Consequently, the burden then shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *de Bazan*, 539 F.3d at 1354; *see also Hammitt*, 98 Fed. Cl. at 726 (explaining that the respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness or condition.'" 42 U.S.C. § 300aa-13(a)(2); *see also Doe v. Sec'y of Health & Human Servs.*, 601 F.3d 1349 (Fed. Cir. 2010) (opining that an idiopathic diagnosis cannot be a "factor unrelated," as it is idiopathic).

VI. Analysis

i. Autoimmune POI

Prior to the entitlement hearing, all of Petitioner's experts noted in one or more of their written reports that Petitioner's condition was an autoimmune POI. In a responsive report, Dr. Wheeler acknowledged that "A.D.'s family history for autoimmune disease . . . certainly put her at risk for the autoimmune thyroiditis and POF she later experienced." Pet'r's Ex. 31 at 3. Dr. Shoenfeld described all POF in his first expert report as "an organ specific (ovary) autoimmune condition." Pet'r's Ex. 50 at 11. And, Dr. Pike wrote that Petitioner "developed autoimmune thyroiditis, Hashimoto's [t]hyroiditis, after vaccination." Pet'r's Ex. 92 at 22. All three experts maintained this opinion throughout their testimony at hearing.

Respondent's experts also initially agreed that Petitioner's POI was autoimmune in nature.[70] Dr. Caturegli's "review of [Petitioner's] records lead[him] to believe that [Petitioner] has an autoimmune condition currently manifesting as ovarian failure and Hashimoto's thyroiditis . . ." Resp't's Ex. A at 2. Dr. Frankfurter also opined that Petitioner's POI "had an etiology [] most likely of an autoimmune nature." Resp't's Ex. C at 4. During the hearing, Dr. Caturegli maintained that position; however, Dr. Frankfurter testified that Petitioner "had an autoimmune process going on, but [he wouldn't] necessarily say this is autoimmune POI." It is unclear why Dr. Frankfurter changed his opinion. He characterized this shift as semantic and maintained that his position did not substantially change. He also conceded that Petitioner's condition could ultimately be characterized as autoimmune if she develops anti-adrenal antibodies.

Dr. Frankfurter's characterization of Petitioner's condition as "POI associated with autoimmune illness," is confusing. He acknowledged that Petitioner "had an autoimmune process

[70] Dr. Cetaruk's expertise is in toxicology and he focused on the effect of aluminum in the vaccine Petitioner received. He did not opine on whether her POI was autoimmune in nature.

going on," but could not explain the distinction that he was making between that an actual autoimmune POI. Unfortunately, Dr. Frankfurter's refusal to acknowledge that there are autoimmune diseases that are definitively diagnosed without a finding of anti-adrenal antibodies undercuts the credibility of his remaining testimony. Dr. Frankfurter testified that he is looking for definitive evidence of damage to Petitioner's ovaries, coupled with organ specific antibodies. He does not provide persuasive literature or medical support for this requirement. Without adequate objective support, Dr. Frankfurter's definition of autoimmune disease does not appear to be the medical standard. Furthermore, he fails to articulate any differences in clinical presentation that this distinction creates. As a preliminary matter, I find that Petitioner presented preponderant evidence that her POI and Hashimoto's thyroiditis are comorbid autoimmune diseases.

ii. *Althen* Prong One

Dr. Shoenfeld identified molecular mimicry, aluminum toxicity, and aluminum adjuvant induced autoimmunity as the three biological mechanisms that together caused Petitioner's autoimmune POI. ASIA is a theory that has been unsuccessfully argued by Dr. Shoenfeld in several previous program cases. He developed this pathogenesis for vaccine injury and has tried with little success to establish that this phenomenon, often in conjunction with molecular mimicry, can result in vaccine-caused autoimmune disease. In fact, the validity of the ASIA theory has been repeatedly called into doubt in the program. *See D'Angiolini v. Sec'y of Health & Human Servs.*, 122 Fed. Cl. 86, 102 (2015) (upholding special master's "determin[ation] that ASIA does not provide[] a biologically plausible theory for recovery"), *aff'd*, 645 Fed. Appx. 1002 (Fed. Cir. 2016); *Garner v. Sec'y of Health & Human Servs.*, No. 15–063V, 2017 WL 1713184, at *8 (Fed. Cl. Spec. Mstr. Mar. 24, 2017) (observing that the ASIA theory "is, at a minimum, incomplete and preliminary—and therefore unreliable from an evidentiary standpoint"); *Rowan v. Sec'y of Health & Human Servs.*, No. 10–272V, 2014 WL 7465661, at *12 (Fed. Cl. Spec. Mstr. Dec. 8, 2014) (rejecting the ASIA theory because it "is not a proven theory" and no "persuasive or reliable evidence" supports it); *Johnson v. Sec'y of Health & Human Servs.*, No. 10–578V, 2016 WL 4917548, at *7–9 (Fed. Cl. Spec. Mstr. Aug. 18, 2016) (rejecting Dr. Shoenfeld's expansive medical theory that "any adjuvant [is] capable of causing any autoimmune disease," finding it "overbroad, generalized, and vague, to the point that it could apply to virtually everyone in the world who received a vaccine containing an adjuvant and then at some time in their lives developed an autoimmune disease"). The primary reason for ASIA's rejection is its "changing and imprecise" diagnostic criteria, which are unable to "distinguish between afflicted and un-afflicted patients." *D'Angiolini*, 122 Fed. Cl. at 102.

In the present case, Dr. Shoenfeld testified that his ASIA theory could be applied to any vaccine and any autoimmune disease that occurred in someone with a genetic predisposition. Tr. 283:4–6. He has presented no new or additional evidence in this case to explain how a patient, treater, or anyone would be able to distinguish an individual suffering from an autoimmune disease due to ASIA from someone who was vaccinated and who subsequently developed an unrelated autoimmune disease. Dr. Shoenfeld dedicated a significant part of his testimony to a discussion regarding medical journal editors and their reluctance to publish unfavorable vaccine research. He expounded on his belief that their refusal to print this type of research generally, and his research specifically, is why ASIA is unable to gain ground in the medical community. He does not, however, support this contention with evidence. His own publications do not prove his causation

theory, and his hypothesis has not been successfully tested by others. Dr. Shoenfeld testified that unlike a Table claim, an actual cause-and-effect relationship was not necessary to establish but-for causation. Instead, he described the standard as plausible or logical. While a theory should be clearly and logically applied to the specific facts in any given claim, Petitioner must first articulate a theory that does show that the "vaccine at issue (can) cause the type of injury alleged[.]" *Pafford* at *4. I find that Petitioner did not establish by a preponderant standard that HAV can cause POI via adjuvant induced autoimmunity solely, or in conjunction with any other mechanism.

Dr. Shoenfeld also testified that Petitioner suffered from some degree of aluminum toxicity. Like his ASIA theory, he was unable to identify any human studies that directly support this theory; he noted however, the impossibility of conducting a study on a condition that is discovered in an individual several years post any relevant vaccination. Studies are not required to establish causation in the program, and I will not hold the lack of studies against Petitioner here.

Dr. Shoenfeld did rely on the published work of Gail DeLong to support his contention that women have become increasingly infertile since the development and widespread administration of the papillomavirus vaccine. He contends that this infertility is caused by the aluminum component of the vaccine on the female reproductive system. Despite no evidence from Dr. DeLong that there were medical limitations on her subjects, Dr. Shoenfeld testified that it is not even plausible that a woman would choose not to have children at the same rate as previous generations. He maintained that position even when he was confronted with evidence that modern women have alternative professional and personal opportunities that may not have been available in the past. Dr. Shoenfeld's refusal to acknowledge the potential impact of changes in female reproductive medicine or economic circumstances, and other alternative causes, before making a determination of causation with respect to Dr. DeLong's work, undercuts his opinions regarding causation here. He recognizes that association is not causation but seems to rely almost entirely on association to establish causation regarding the infertility of women in the general population. Although plausibility is not the standard, Dr. Shoenfeld's assertion that aluminum toxicity is a plausible mechanism is not persuasive.

Dr. Pike presented evidence on "what efforts have been undertaken to determine the safety of adjuvants used in vaccines." *See* Pet'r's Ex. 92 at 2. The studies that Dr. Pike discussed establish that aluminum in large amounts can be harmful to certain animals, particularly in gonads. These studies, however, involve doses of aluminum administered consistently over a period of time. Dr. Pike's testimony reiterated that there have been no studies conducted on humans to illustrate the types of harmful effects that he or Dr. Shoenfeld described. As Dr. Cetaruk noted, the human studies presented by Petitioner discuss occupational exposure to aluminum, also occurring over an extended period of time. More importantly, they do not show reproductive system pathology. Likewise, the study on the effects of drinking water contaminated with various metals in Brazil revealed adverse effects, but there was no correlation between the levels of aluminum and reproductive pathology. Based on this study, Dr. Pike overreached with his conclusion that aluminum exposure specifically can cause neurological, neurobehavioral and cognitive impairment. Furthermore, the children in the Brazilian study, like the workers, were exposed to the metals over time. There were no studies that illustrate adverse effects on reproductive health in humans following acute aluminum exposure.

To explain the lack of human studies, Dr. Pike pointed to the rarity of (1) the types of autoimmune conditions that Petitioner developed and (2) the presence of multiple cofactors/susceptibility in the same person. As Respondent's experts noted, there are problems with extrapolating conclusions from the animal studies due to the differences between the animal and human physiology, the different methods of administration, the variance in dosage, and the length of exposure. Dr. Pike dismissed these factors. Specifically, he characterized the fact that these studies are based on cumulative doses instead of the type of acute exposure that results from vaccination as irrelevant. This dismissal was conclusory, and Dr. Pike did not adequately explain why the variance in dosing should not be considered. Therefore, I do not find his use of these studies persuasive. Additionally, Dr. Pike does not adequately explain why Petitioner did not suffer from adverse effects of aluminum toxicity following prior exposure to aluminum, including the battery of vaccines she received as a younger child. I do not find that Dr. Shoenfeld and Dr. Pike provided preponderant evidence that aluminum toxicity, solely or in conjunction with any other mechanism, can cause POI.

Petitioner argues that in addition to ASIA and aluminum toxicity, molecular mimicry contributed to the development of her POI. Petitioners are not expected to provide specifics of the biological mechanism that explains their disease pathology; however, to the extent that they do, it must make sense. To support a molecular mimicry theory in this case, Dr. Shoenfeld identified a hexapeptide, REAGRI, that is present in the helicase MCM8 and in HAV. He explained that the MCM8 gene is essential to ovarian function and maturity. Furthermore, a MCM8 gene mutation is often seen in chromosomal and genetic disorders that lead to POI. REAGRI, while not an especially long hexapeptide chain, appears in an enzyme that regulates the protection and maturity of oocytes. It follows that if the Petitioner's immune system reacted to the REAGRI hexapeptide in the MCM8 helicase instead of HAV, this autoimmune attack could cause MCM8 gene dysfunction. I find Petitioner has presented preponderant evidence to show that cross-reactivity between a component of HAV and MCM8 could result in ovarian insufficiency or failure.

Dr. Shoenfeld presented persuasive evidence that molecular mimicry was a substantial factor in the development of Petitioner's POI. Petitioner has established that it is more likely than not that molecular mimicry can be a substantial factor in the development of POI following HAV vaccination in an already susceptible individual. I find that the role of aluminum as an adjuvant in this case did not further add to this mechanism.

Respondent's arguments against Dr. Shoenfeld's ASIA theory and Dr. Pike's aluminum toxicity theory are persuasive; however, Respondent's assertion that there are no studies to illustrate molecular mimicry with respect to HAV and POI highlights the nature of this Program and the rarity of the conditions we see. POI in very young girls is so rare, the ability to conduct any sort of study in that patient demographic is difficult. This would be compounded by Respondent's assertion that invasive testing is needed to confirm a true case of autoimmune POI. I do not find persuasive Respondent's argument that because we have not seen this occur often, it did not occur here.

Both of Respondent's experts disagreed that molecular mimicry is a viable mechanism in this case. Dr. Caturegli described molecular mimicry as "very attractive intellectually." Tr. 435:7. He went on to say that most articles that discuss the phenomenon are thought or conceptual essays.

Dr. Caturegli downplayed the work of leading experts in the field because of the lack of studies establishing that a specific peptide sequence can consistently cause a specific pathological result. Again, Respondent places a premium on epidemiological studies while simultaneously conceding the rarity of Petitioner's circumstances.

Dr. Frankfurter criticized the applicability of molecular mimicry in this case given Petitioner's identification of a peptide chain that only contains five amino acids. Respondent is correct that a simple blast search will likely always reveal a match of several or more, short hexapeptide chains, but they are usually, if ever, responsible for an essential function. When asked about the amino acids identified in this case, Respondent conceded their role in oocytes maturation but claimed that the chain played no further role in egg maturation once a female began menstruation. Respondent has not presented a persuasive argument that establishes the basis for his conclusion. His assertion relies on as much speculation about the role of MCM8 as Petitioner's argument. I do not find that Respondent successfully rebutted Petitioner's argument regarding the potential for cross-reactivity of these amino acids.

Petitioner presented evidence that HAV can cause autoimmune POI via three mechanisms working in tandem. I do not find she met her burden that POI can be caused in whole or in part by aluminum adjuvant induced autoimmunity or aluminum toxicity. I do find that Petitioner established by a preponderant standard that molecular mimicry in a susceptible individual can cause HAV-induced, autoimmune POI.

iii. *Althen* Prong Two

All of the experts in this case agree that Petitioner's case is an example of one of the rarest manifestations of an already uncommon disease. Dr. Wheeler noted that this condition is extremely rare in teenagers and difficult to diagnose. He concluded in his expert report that although a temporal relationship is not enough to establish causation, "in the absence of other known causes, and the presence of strong evidence of autoimmunity, then an autoimmune cause becomes the most probable." Pet'r's Ex. 23 at 9. There were no studies submitted that successfully identified a pathogenesis consistent with Petitioner's progression. There has been persuasive evidence presented that Petitioner is predisposed to autoimmune disease. Such an individual would be at higher risk for developing an autoimmune disease following an immune response, such as a vaccination. Petitioner's development of POI was fairly rapid, which is also indicative of a trigger. Respondent's reliance on evidence of Petitioner's slowed growth to suggest her POI manifested prior to vaccination is not persuasive, given that Petitioner remained within normal growth range.

Respondent's rebuttal is also hampered by the contradictory positions that both Drs. Caturegli and Frankfurter espoused. Dr. Caturegli testified that although he believed at the time he wrote his report that POI is autoimmune, he is not an expert. He retracted that conclusion during his testimony and stated that he likely made a mistake using that characterization. Likewise, in his written report, Dr. Frankfurter indicated that Petitioner's POI is autoimmune in etiology. He later took a more equivocal position, and it remains unclear the difference between what he called autoimmune POI in his report and POI with "autoimmune involvement," as described in his testimony. Tr. 336:14. Respondent's experts appear to backtrack here because conceding that POI is autoimmune provides the necessary prerequisite circumstances for Petitioner's claim of vaccine

causation. Petitioner has a predisposition to autoimmune disease and developed a very rare condition under very abnormal circumstances, following an immune system event. It is possible that Petitioner may have developed POI later in life, given her Hashimoto's thyroiditis diagnosis; however, she did not. Respondent's assertion that her case is idiopathic because most cases are, is not persuasive.

I find that Petitioner has established by a preponderance of the evidence that because of her susceptibility to an autoimmune event, the immune response triggered by HAV resulted in molecular mimicry, thereby causing her to develop POI.

iv. *Althen* Prong Three

Petitioner has met her burden with respect to *Althen* prongs one and two. Finally, she must establish that there is an appropriate temporal relationship between her HAV and the development of her POI. There was some dispute among the experts regarding the onset of Petitioner's POI that is further complicated by her comorbid Hashimoto's thyroiditis diagnosis. Dr. Shoenfeld testified that there is an appropriate temporal relationship between Petitioner's HAV and the onset of her POI, but he has suggested that conditions that develop post-vaccination and pursuant to ASIA can take weeks to months. With this broad timeline, there does not appear to be a circumstance wherein he would not find an appropriate relationship. Ultimately, Dr. Shoenfeld testified that the timeframe in Petitioner's case from vaccination to POI diagnosis "ranges between three weeks, one month to two months, which is usually the timeframe, that is asked, demanded by the Court." Tr. 245:4–9. This timeframe is based on what is accepted by the Court for other vaccine-induced autoimmune diseases, including the flu-GBS Table claim. Dr. Shoenfeld opined that this timeframe was sufficient for the "binding of the autoantibody to the organ and eventual development of enough damage to the organ to be represented." Tr. 250:4–7.

Dr. Pike used a bee sting analogy to illustrate how an appropriate temporal relationship between acute exposure to an allergen and an immune reaction can establish causality. This sequence of cause and effect only works when the system response to the stimulus is immediate. POI, the disease at issue here, is a condition that develops over time, often with intervening factors not present in the case of an immediate bee sting reaction. Dr. Wheeler presented evidence that the damage to Petitioner's ovaries was akin to a poisoning that was not acute but that happened over time. This time period of a few months is compressed when compared to naturally occurring menopause experienced by older women over the course of years. This time period is also consistent with an autoimmune response to a trigger such as vaccination.

Respondent's experts were also inconsistent when it came to the temporal relationship between Petitioner's vaccination and diagnosis. On one hand, Dr. Frankfurter noted that Petitioner's first symptom of an irregular menstrual cycle occurred too quickly post-vaccination. On the other hand, Dr. Frankfurter testified that Petitioner may have had estrogen level fluctuations, which would be a symptom of her developing POI, approximately one-year pre-vaccination. There was no evidence presented that Petitioner's growth was affected by changes in estrogen levels. Furthermore, Dr. Frankfurter ultimately conceded that two weeks is enough time for antibody production to initiate an autoimmune process. When asked why two weeks would not be enough in this case, he opined that there are too many HAVs administered ("hundreds of

millions throughout the history of the virus") to have not seen an increase in gonadal dysfunction. Tr. 373:21–23. This argument acknowledges the uniqueness of this situation. The same question could be generally asked: why did Petitioner's condition manifest in a way so rarely seen?

I find that Petitioner has presented preponderant evidence to establish that two to six weeks is an appropriate timeframe for vaccine-induced POI to occur in Petitioner's case.

IV. Conclusion

This case presented a one-in-a-million, perfect storm that resulted in unimaginable loss for Petitioner and her family. Ultimately, Petitioner has established with preponderant evidence that the Hepatitis A vaccine she received on July 16, 2013, was a substantial factor in the development of her premature ovarian failure. Petitioner did not present sufficient evidence that all three components of her theory worked together. In fact, Dr. Shoenfeld's reasoning with respect to ASIA detracts significantly from Petitioner's claim. Dr. Pike's aluminum toxicity evidence is also not compelling enough to meet the more likely than not standard. Petitioner did not argue that molecular mimicry alone is sufficient to cause her POI. However, the evidence in the record supports a finding that more likely than not, molecular mimicry caused Petitioner to develop POI following her HAV. The evidence Petitioner presented has therefore demonstrated entitlement to compensation. This case shall proceed to damages.

IT IS SO ORDERED.

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master